

Clinical Research

PROCEEDINGS

Official Publication of The American Federation for Clinical Research

VOL. III, NO. 4

NOVEMBER, 1955

REFERENCE SET
NON-CIRCULATING

IN THIS ISSUE

STATISTICS, SOPHISTICATION, SOPHISTRY AND SACRED COWS, *page 185*

THE NEW LOOK IN MEDICAL GENETICS, *page 187*

NOTICES, *page 191*

PROGRAM, *page 192*

ADVANCE RESEARCH REPORTS SUBMITTED TO THE ANNUAL MEETING
OF THE MIDWESTERN SECTION, AMERICAN FEDERATION FOR CLINICAL
RESEARCH, CHICAGO, NOVEMBER 1955. *page 194*

ANNUAL AUTHOR INDEX, *page 215*

ANNUAL SUBJECT INDEX, *page 219*

Published by Grune & Stratton, Inc.



Statistics, Sophistication, Sophistry and Sacred Cows

By Louis Lasagna*

WE ARE ALL SNOBS,[†] of course. The ego, sometimes referred to as a fragile gossamer thing, actually has an omnivorous appetite. It subsists on a diet of favorable comparisons with other egos over which it possesses a real or imagined superiority. Medical research has always provided a bounteous banquet-table for starved egos, but in recent years has begun to nourish in greater numbers persons whom I shall call Statistical Snobs.

There are two main varieties of Statistical Snobs. The first of these is the Professional Illiterate, or Statistical Hayseed. He professes a great disdain for all statistics, and boasts of his ignorance of statistical principles and technics. In ghoulish glee, he points to such books as *How to Lie with Statistics*,¹ and reminds you that "you can prove anything with statistics," or (on alternate days) that "nothing has ever been proven with statistics." He sneers at the "Ivory Tower Boys" who "just don't realize what the practice of medicine and the problems of clinical research amount to." He is shocked at the thought of controlled experiments, where some patients receive placebos and are thus "denied the benefits of treatment." (With typical largesse, this objection is levelled at all treatments, be they established ones of proven efficacy, or untested drugs or procedures which not infrequently turn out to be more deleterious than no treatment at all.) He is fond of writing papers (summarizing uncontrolled observations) which he admits are inconclusive, but usually end with: "The results are promising and warrant further investigation." His prevailing philosophy ranges from absolute nihilism to rapid and complete ingestion (sans mastication) of new claims, since he lacks any standard of reference for evaluation other than an ill-defined, ectoplasmic link with the Unknown referred to as My Clinical Judgment, or My Past Experience. These individuals, while all too real, are an old phenomenon on the American scene, and actually less annoying in some respects than the

second major type of Statistical Snob—the Chi Square Cavalier.

The Chi Square Cavalier, or T-test Terror, is a crusader for statistics in the scientific world. To him a paper without at least one probability value is a shuddery concept. As rigidly doctrinaire as the Statistical Hayseed, he would apply his technic to all data, even when it is not desirable or possible to do so. Since many of these Cavaliers know only enough statistics to impress those who know none at all, some rather amusing things occur at times. Data which have been collected in such a way that comparison of treatments is meaningless are subjected to exhaustive scrutiny. Matched data are treated as independent data, or vice versa. Large sample technics are applied to samples of microscopic size. A moderate amount of knowledge in this field is not, however, an impregnable bulwark against error. As a matter of fact, a special type of mistake is probably most commonly committed by a more advanced group of Chi Square Cavaliers.

The error to which I refer is the Microstatistical Mirage. Papers may be found in which "highly significant differences" are described, but which on careful reading seem to be concerned with extremely small differences which have been shown to be significant only by the use of very large samples. Several examples may help to illustrate the field of Microstatistics[‡]:

One paper reported the results of a study of antitussive drugs. The numeric scale for the severity of cough was from 0 to 4, as follows: 0, indicating no cough; 1, occasional, barely troublesome cough; 2, moderately troublesome cough; 3, markedly troublesome cough; and 4, incessant and distressing cough. Eleven thousand observations were made, with "highly significant" differences being established between treatments. When one looks at the figures, however, it is interesting to see that the most "potent" drug studied (codeine) caused a drop in mean severity of cough (from the 1st to the 5th days

* Departments of Medicine and Pharmacology, Johns Hopkins School of Medicine, Baltimore, Maryland.

† With apologies to Russell Lynes.

‡ I hope that those statisticians who refer to the statistics of small samples as microstatistics will excuse the above usage.

of observation) from 1.33 to 1.09, whereas the placebo caused a change from 1.58 to 1.53. Obviously the average severity of cough studied was mild, and the mean decrement after treatment small indeed.

Another paper was concerned with the calming effect of Rauwolfia on a group of agitated psychotics. Again we find large numbers of observations made (over 400 patients were studied), with the following "highly significant" results:

	Premedication	Placebo	Rauwolfia	Serpasil
% Noisy	19	19	15	14

The difference between the Rauwolfia and non-Rauwolfia conditions . . . is significant at the 1 per cent level of confidence.

Without denying the validity of small differences, one wonders whether the cause of progress is not better served in such instances by accenting the essential *insignificance* (from a practical standpoint) of such results.

The antipode of the Microstatistical Approach is presented by the Tunnel Vision (or Close-But-No-Cigar) School, members of which steadfastly refuse to call any attention to differences which do not reach some mystic probability level, no matter how close they may come to achieving this point. Even when a small series has been studied, and there is good reason to suppose that a few more cases would have allowed penetration through the Magic Wall of p. 0.05 Fire, we find the observed differences being curtly dismissed as "not significantly different." As Kennaway has recently pointed out,² there are very interesting examples of minute (but important) small differences which are almost impossible to demonstrate "statistically" under ordinary circumstances. He cites Haldane to the effect that the increase in length of ceratopsian dinosaurs from 1.7 to 6.5 meters in 22 million years took place (at the beginning of the period) at the rate of 1 mm. per 10,000 years. One can picture an early caveman snob telling another caveman that "All this rot about the dinosaurs getting bigger is just erroneous clinical impression, old man."

Another kind of Statistical Snob is the Placebo Pusher (or Double Blind Dodo). Having learned the magic words "placebo" and "double blind," this species insists that any report in the literature not containing these controls constitutes a complete waste of everyone's time.

If some happy clinician reports twelve cases of pathologically proven metastatic carcinoma cured within two weeks by some new drug, with maintained cure for ten years, the Dodo screams for "placebo controls." If someone reports a series of 50 cases of staphylococcal meningitis, randomly distributed to two treatment groups, with 90% survival in one and 0% in the other, the Dodo sneers, "Were the people involved in making the value judgments

as to life or death kept unawares of the nature of the two medications, and did the patients know which drug they were getting?"

Like all militantly dogmatic groups, the Placebo Pushers are blissfully unaware of certain incongruities in their attitudes. For example, if one is studying the effects of nicotinic acid, injected intravenously, on headache, it is difficult to keep the injector in the dark as to which medications are nicotinic acid and which are saline, unless he is physiologically blind. (It would also help if he were deaf, so as not to hear the patient's comments.) One can get around this problem by using one person to inject and another person to evaluate the results, but how does one fool the *patient* in this case? The patient who has just got a big dose of nicotinic acid (or apomorphine, or veratrum) will usually have little difficulty in distinguishing such injections from saline.

The Placebo Pusher also has his counterpart among the nonbelievers. One recent study concerned itself with the analgesic effects of aspirin in a group of patients with chronic complaints referable to the musculoskeletal system. Having failed to show a difference between placebo and aspirin, the authors came to the astonishing conclusion that the double blind technic was not suited to the demonstration that aspirin was an analgesic drug in patients of this sort! This statement would seem equivalent to borrowing the favorite rifle of a crack marksman, missing the target, and then blaming the poor performance on the gun.

A final bit of Statistical Snobbery will be included because of its direct significance for the writer of this paper. Recently, I discussed a large series of patients who were subjected to portocaval shunts. During the early years of experience with this technic (the same surgeon did all the cases) one type of anesthesia was employed. During the later years, a second type of anesthesia became the preferred one. Since the passage of time was also associated with changes in patient selection, surgical technic, use of fresh blood, etc., I suggested that it would actually be more sophisticated for the authors to describe the results as "our experience during the first two years" and "our experience during the last two years," rather than analyze the data statistically for differences in morbidity and mortality, with an eye toward comparing the two anesthetic agents in this procedure. One critic commented that there was no point in publishing data such as these. I could hardly disagree more. Any doctor with a patient or relative with cirrhosis of the liver would be most interested to know that, as of 1955, there is a surgeon around capable of doing portocaval shunts with a very low mortality, regardless of whether he is able to put his finger on the reasons for the low mortality, and regardless of whether he can learn from the data in the paper if ether and cyclopropane differ in their safety in this situation.

As is all too obvious, some of the descriptions above have been purposely exaggerated. These parodies are intended to emphasize certain errors which are met with all too frequently at meetings and in articles. As with most things, almost every point which has been attacked has much merit per se. In the blind or rigid application of even praiseworthy principles, however, ridiculous excesses creep in. Having been personally guilty, at one time or another, of most of the foibles satirized here, I feel considerable freedom in directing these remarks to

any fellow sinners in the audience. The comments are presented not so much in the nature of stone-casting as to indicate the extreme vulnerability of the Statistical Snob to criticism by the Editorializing (or Converted Sinner) Snob.

REFERENCES

1. HUFF, D.: *How to Lie with Statistics*. New York, W. W. Norton, 1954.
2. KENNAWAY, E.: The statistical significance of biological data. *Brit. Med. J.* **2**: 663, 1954.

The New Look in Medical Genetics

By Victor A. McKusick*

ALTHOUGH THE PEDIGREE METHOD is still the basic technic, new methods, new twists on old methods, and enlightening developments in some closely related fields make medical genetics, and human heredity in general, currently exciting fields of investigation. It is worthwhile to survey briefly those areas in which there is now much activity, to consider in general the assets and liabilities of man as an object of genetic study, to point out some of the misconceptions about genetics to which medical folk are prone, and finally to indicate areas in which, to my mind, investigation should, and can with profit, be pursued.

Currently Active Areas of Investigation

(1) *Cytologic studies* with conspicuous genetic implications include the demonstration in man of sex differences in the nucleus of epidermal and other cells by Barr,¹ and of polymorphonuclear leukocytes by Davidson, and the dramatic displays of the human chromosomes by Hsu. The cytologic determination of sex has been put to use in connection with a group of patients previously labeled ovarian agenesis (Turner's syndrome), now labeled gonadal dysgenesis; and it has been demonstrated that many of these individuals are in fact males.

(2) In the study of the mechanisms of gene action in human diseases (so-called physiologic genetics) and in the related search for a common denominator in the many complex hereditary syndromes of man, fascinating developments have been forthcoming. Investigations of this type are often doubly significant because identification of the component in the machinery which is "out of kilter" so often points to

normal mechanisms that were previously obscure. For example, Wilson's disease, hitherto a perplexing combination of hepatic and central nervous dysfunction has now been identified as a defect in the synthesis of ceruloplasmin, a serum globulin which binds copper, thereby preventing its deposition in the tissues. Osteogenesis imperfecta appears to be a defect in the maturation of collagen beyond the reticulin stage.

Many hereditary syndromes can be convincingly identified as resulting from a single mutant gene, even though the basic defect responsible for the seemingly diverse components remains mysterious. Why does one mutant gene result in garden-variety adenomatous polyps of the small intestine and melanin spots of the buccal mucosa, lips and digits? What do the media of the aorta and the suspensory ligament of the lens have in common that leads to disruption of both in Marfan's syndrome? Why should a double row of eyelashes (districhiasis) have a syndromal association with lymphedema of legs (Milroy's disease) in some cases and, in other cases, congenital ptosis and lymphedema be related? Why do retinitis pigmentosa, polydactyly, mental retardation, obesity and sexual infantilism (Laurence-Moon-Biedl syndrome) occur together? Why the association of dextrocardia, bronchiectasis and sinusitis (Kartagener's syndrome); of dystrophy of the nails and congenital defect of the patella, and so on? A greater understanding of human embryology would solve some of these mysteries. Conversely, however, these abnormalities may conceivably shed light on normal development, that is, can, in effect, be investigative tools.

As clinicians, we are continually forced to think in terms of the total patient. This is also true of hereditary anomalies. The surgeon cannot look on

* Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland.

pulmonary arteriovenous fistula as a local lesion, since it is frequently only one manifestation that dominates the clinical picture in Rendu-Osler-Weber's multiple telangiectasia. The same is true of polycystic disease of viscera. The ingenious suggestion has been made that an hereditary anomaly of the mucous gland of the entodermal tube, and its derivatives, results in an abnormal secretion which is responsible for cystic fibrosis of the pancreas, celiac disease, meconium ileus and, possibly, biliary obstruction; in the respiratory tract, the clinicopathologic end-products are emphysema, bronchiectasis or lung abscesses. The whole syndrome is referred to as "mucoviscidosis." This type of thinking is bound to be profitable, if care is taken to distinguish hypothesis from proven fact, and to follow up promising hypotheses with pertinent evidence—observational or experimental.

(3) Closely related to identification of the fundamental defect in genetic disorders is *the development of the methods for detecting the heterozygous carrier of the gene for a recessive trait*. In sickle cell anemia (a recessive trait in the sense that "disease" occurs only in the homozygote), an asymptomatic abnormality of the red cell is the identifying feature of the heterozygote. Similarly, ovalocytosis is an asymptomatic condition of no apparent clinical significance when the trait occurs in the heterozygous state, whereas in the homozygote it is associated with hemolytic anemia. In few other recessive conditions, however, can we now recognize the heterozygote, although progress is being made. Sacks has recently identified, in a hemorrhagic diathesis which is inherited as an autosomal recessive and is due to deficiency of proaccelerin factor, an intermediate degree of deficiency—insufficient to effect the clotting mechanism—in the heterozygous parents of affected individuals. Potentially, this approach has practical usefulness in connection with genetic prognostication and counseling.

More than brief mention of the important studies of population genetics, with ramifications into the background of the races of man, will be omitted since the purely medical implications are not immediately apparent.

Assets and Liabilities in Man as an Object of Genetic Study

Certain advantages of the several "classic" species (*Drosophila*, corn, neurospora, etc.) employed in experimental genetics are not realized in the case of man. Matings at will are not possible, nor can one control environmental factors with exactitude. Furthermore, the very fact that man has 24 pairs of chromosomes and an estimated 40,000 to 80,000 genes indicates the complexity of genetic analysis. Embryogenesis is studied with difficulty in man. The small number of progeny from a given mating and the length of individual generations and

life-spans are considerable handicaps. Consider the difficulties encountered in studying the inheritance of Paget's disease or pernicious anemia, or of any disease which is one of senescence or which expresses itself only in the third or fourth decade. By the time an individual develops recognizable disease, it is likely that the parents will be dead, the siblings will be dead or scattered widely geographically and the offspring will not yet be old enough to have developed the disease.

There are also great advantages to the study of genetics in man. About no other organism has such a vast body of information—anatomic, chemical, physiologic, psychologic, pathologic—been accumulated. The small numbers of generations available for direct study within a reasonable length of time are supplemented by long records compiled by man, whose egocentricity and curiosity about himself are limitless. For economic reasons pathologic traits in animals are not studied to any significant extent. A genetically diseased animal is likely to be destroyed, and information about the trait not put on public record for fear of damaging the reputation of the breed.

The small number of progeny from a given human mating can be circumvented by the study of population groups. Although matings cannot be produced at will, it is often possible to discover chance matings of the type desired. In the case of many hereditary diseases, what is seemingly precisely the same disorder—same biochemical defect, same phenotypic syndrome, same mode of mendelian inheritance—is present in animals. Examples are hemophilia of dogs, Pelger-Huet anomaly of the leukocyte in rabbits,² ateleiotic dwarfism in fowls, Jersey cattle, spaniel dogs, etc., alcaptonuria in rabbits, and hare-lip in mice. In such instances the disease in man can guide investigations in animals, and results can be transferred back to man with some confidence.

As physicians we are in an enviable position as far as the study of genetics in man is concerned. Our knowledge of human biology is part of the advantage. In addition, the motivation of illness renders the patient and his family unusually willing to permit, and to cooperate in, investigations of genetic factors. More and more, with the passage of time, it will be possible for us to "cash in" on the careful records kept in the archives of our hospitals and clinics. For example, a patient recently presented himself to the Johns Hopkins Hospital because of symptoms suggesting "brain tumor." The mother died at the same hospital in 1916 of brain tumor. Examination of the history and of the autopsy material in the case of the mother revealed that she suffered from Von Hippel-Lindau's syndrome. Therefore, it was possible in the case of the son to predict the histologic nature of the tumor before craniotomy.

Misconceptions about Medical Genetics

Possibly one of the most widespread misconceptions about the clinical behavior of hereditary diseases is the belief in the unpredictability of their manifestations. I recently read a paper on cardiovascular aspects of Marfan's syndrome at a national medical meeting. During the preceding paper this conversation was overheard: "What happens to the heart in Marfan's syndrome?" said one, obviously looking ahead on his program. His fellow replied, "Oh, that is one of those congenital-familial affairs in which anything can happen." Worthy of emphasis is the direct corollary of the hypothesis that a given disease is the result of a single mutant gene: the clinical picture in each hereditary syndrome is as clear-cut and specific (with, of course, the variability which we as clinicians learn to expect) as the clinical picture produced by a pathogenic microorganism. In many respects hereditary disease differs from infectious disease only in that the etiologic agent is a mutant gene operating from within rather than a bacterium invading from without. The virologists have long been aware of the basic analogies between genes and viruses. Viruses have even been pictured as lost souls of genes, wandering aimlessly in search of a chromosome.

A second misconception seems almost absurd: that those hereditary diseases which occur relatively frequently display a dominant pattern of inheritance and that rare hereditary disorders are recessive. Speaking in terms of gene frequency, even for rarer conditions with recessive mode of inheritance there is a relatively high incidence of the gene in the general population. For instance, about one person in 70 carries a gene for albinism. That albinism occurs only about once in 20,000 individuals is merely because two genes for the trait must coincide in an individual for the condition to be clinically recognizable. Contrariwise, the gene frequency for a dominant trait such as Marfan's syndrome is virtually the same as the incidence of the disease itself, a very low figure. R. A. Fisher² has suggested that the mode of inheritance of a disease trait tends to undergo evolution with progression from dominance to recessivity. It is reasonable to believe that natural selection would result in survival of, and procreation by, individuals in whom the rest of the genetic milieu favored mild expression of the trait, particularly in the heterozygote. In time, no expression would occur in the heterozygote (the situation referred to as recessive inheritance). In keeping with this idea is the fact that, by and large, traits with a high mutation rate—traits which are, therefore, early in their evolutionary progression—are dominant. Furthermore, traits which represent no peril to reproductivity and survival tend to remain dominant. For example, examination of the skeleton of John Talbot, the first Earl of Shrewsbury, who died in 1453, revealed the same syndactyly as his direct

descendants fourteen generations and five centuries later. In the case of the so-called abiotrophies, age of onset of clinical manifestations tends to be earlier when the trait is inherited as a recessive than when it is inherited as a dominant.

A final common misconception is that hereditary disease is by its very nature untreatable and therefore unworthy of study by the physician. The case of phenylpyruvic oligophrenia is a good example of the way in which investigation of an hereditary disease can, under favorable circumstances, proceed. First came the description of the clinical picture and of the empirically associated diagnostic test; then the demonstration of the hereditary nature and the mode of inheritance; then the precise enzymatic defect was worked out; and most recently the path to successful treatment of these cases by restriction of phenylalanine has been pointed out.

Areas of Medical Genetics to be Cultivated

The following is a very incomplete enumeration of promising areas in the general field of medical genetics:

(1) Cytologic studies of the human chromosome by methods such as those of T. C. Hsu should be performed in diseases of man.

(2) Virtually nothing has been accomplished in the mapping of the human chromosomes. It could be very useful in the genetic counseling of a given family to know, for example, that the gene for certain blood groups is located on the same chromosome as that for a disease trait. Such mapping involves study of gene linkage. Roberts⁴ has pointed out that conclusions about gene linkage can be made from small bodies of data, such as can be accumulated by the busy practicing physician. This is so because gene linkage must be studied mainly in individual families. The many blood groups, ability to taste phenylthiourea, and other traits, can be used as marker genes. In general, however, linkage studies are far from easy. Relatively few marker genes of wide distribution in the population are known. For the method to be useful, at least 10 or 12 markers for *each* chromosome should be available!

(3) Identification of the basic defect of many more single-gene hereditary disorders must be made. This is one of the most fascinating and important areas of genetic research in man—fascinating because revealed by such studies are normal biologic mechanisms, important because such information may provide the background for control of these diseases. Inevitably, bringing many new technics to bear on this type of problem will be helpful in elucidation both of the mechanics of inheritance and of the nature of the basic defect. In relation to the heritable disorders of connective tissue in man, studies of the behavior in tissue culture of fibroblasts from patients with the several disorders might be very enlightening. Similarly, skeletal muscle grown *in vitro* from

cases of muscular dystrophy could be subjected to study from many points of view.

(4) One subject which has scarcely been touched is the development of methods for recognizing the presence of an abiotrophy in an individual before the development of the usual clinical manifestations. In Huntington's chorea, electroencephalographic anomalies have been detected in individuals who at the time were ostensibly normal but later developed the full-blown syndrome. In Wilson's disease the defect in copper metabolism can be detected and treatment with BAL instituted before liver and cerebral damage ensue. In pernicious anemia, a defect in the absorption of vitamin B₁₂ may be present from birth. Like the detection of heterozygous carriers of recessive genes for disease traits, this particular area of human genetics has great practical usefulness.

(5) Constitutional factors in susceptibility to disease have long been tacitly accepted by the physician. This factor is implicitly expressed in such references as "coronary type," "ulcer type," "phthisical constitution," etc. A fascinating recent study is that of Lea⁵ who investigated the incidence of nutritional cirrhosis among former British prisoners of war. This study revealed an impressive preponderance of cirrhosis in the group of individuals of dark eye and hair color. This type of investigation should be extended considerably; it is to be hoped that methods will become available for investigating the mechanisms of these human variations in constitutional susceptibility to acquired disease.

One might mention many other subjects deserving of intensive cultivation: Is cytoplasmic inheritance a significant factor in man? How do genes function in human embryogenesis to result in the changes observed? What genetic factors are operating in congenital malformations and in abortions? What are the factors in mutagenesis in man (such as diagnostic and therapeutic x-ray, and chemical agents such as the nitrogen mustards)? What are the

factors responsible for the pronounced variability in expressivity (clinical severity) of a particular disease trait?

With development of methods for control of the two other largest general etiologic factors in disease—infection and malnutrition—genetic factors become the largest single etiologic influence in disease. Holtz made the estimate that in Norway genetic factors are of *primary* etiologic importance in 49% of cases of blindness. Take, if you will, cardiovascular disease as another general case in point. Each of the three major etiologic categories—arteriosclerosis, hypertension, rheumatic fever—is thought to have conspicuous genetic factors in its background. In reading Knut Faber's classic *Nosography*, it is impressive to find that the Copenhagen professor gave Mendel a leading place among the giants, like Sydenham, Laennec, Virchow, Pasteur, Koch, who shaped modern thinking about the nature and classification of disease. Thinking along genetic lines cuts across every preclinical and clinical division of medicine. Every clinical specialty has fascinating genetic problems awaiting study.

REFERENCES

1. BARR, M. L., BERTRAM, L. F. AND LINDSAY, H. A.: The morphology of the nerve cell nucleus, according to sex. *Anat. Rec.* **107**: 283, 1950.
2. HAVERKAMP BEGEMANN, N. AND LOOKEREN CAMPAGNE, A. VAN: Homozygous form of Pelger-Huet's nuclear anomaly in man. *Acta haematol.* **7**: 295, 1952.
3. FISHER, R. A.: *The Genetical Theory of Natural Selection*. Oxford, Clarendon Press, 1930.
4. ROBERTS, J. A. F.: Genetic linkage in man, with particular reference to the usefulness of very small bodies of data. *Quart. J. Med.* **14**: 27, 1945.
5. LEA, A. J.: Evidence of an inherited factor in trophopathic hepatitis. *Brit. J. Nutrition* **7**: 224, 1953.

NOTICES

Presidential Report: Carleton B. Chapman, M.D.

Security Resolution

The members of the AMERICAN FEDERATION have approved the resolution printed below concerning security proceedings in connection with non-classified government research grants.

The resolution was prepared by the Council on the basis of information collected immediately after the national meeting last May. There was no serious disapproval on principle among the various Council members although there were various views as to wording. The final motion was formulated by Drs. Robert Glaser and Albert Mendeloff, with the help and advice of Dr. David Graham. It was approved by the Council before being submitted to the membership.

The final tabulation will be published in the next issue of CLINICAL RESEARCH PROCEEDINGS.

The Resolution

- I. The American Federation for Clinical Research recognizes the right of the Federal Government to control the granting of its funds for support of scientific research. Furthermore, it understands the need of the most stringent clearance procedures, even though they be nonjudicial and arbitrary, insofar as the selection of investigators to carry out *classified research* is concerned.
- II. On the other hand, with respect to the support of *nonclassified* research, the members of the American Federation for Clinical Research express their disapproval of the present policy of the United States Public Health Service in denying new grants or terminating old ones because of *alleged* subversive activities by the investigators. It should be clearly understood that this objection does not impugn the basic motives underlying this policy. It is our belief that, unless an applicant or grantee can be shown to fall into one of the four categories of truly disloyal persons as defined by the Na-

tional Science Foundation, the allocation of funds for nonclassified research should be based only upon the excellence of the project proposal and the professional and technical competence of the investigator.

- III. The American Federation for Clinical Research endorses the action of President Eisenhower in having requested the National Academy of Science to appoint a committee to counsel with the Government on the matter discussed in Section II above, and expresses its confidence in the membership of the committee appointed by the National Academy.

1956 National Meeting

With regard to the plan for the 1956 meeting, the choice of the members seems to lie between holding the meeting exactly as was done in 1955, or holding specialty meetings on Saturday afternoon and the regular meeting on Sunday. Only 19 members favored breaking the Sunday session up into a number of specialty meetings. The practice of inviting guest speakers to review previously presented work at the specialty meetings has come under fire from several members who have written to the President on the subject. Further correspondence on the point is invited and the whole subject will be reviewed by the Council before the form of the 1956 meeting is finally set.

Members' Opinions

The Council and officers are very anxious to serve the organization as effectively as possible and wish to encourage individual members to express their views by letter and at the various meetings. Since ours is a growing and vigorous organization, differences of opinion are confidently to be expected. Every effort is made, however, to settle such differences judiciously, and the interest of the individual member in the welfare of the organization is earnestly solicited.

Membership

The AMERICAN FEDERATION FOR CLINICAL RESEARCH is an organization which has as its main purpose the encouragement of clinical investigation by young workers. It does not, however, favor any specialty group over any other; membership is open to anyone who is engaged in clinical research provided he meets the basic qualifications required by the constitution. The tendency in the past for the organization to be made up mainly of internists has not been by design, and a broadening of its representation in the various specialties is currently being sought. The council wishes to encourage the submission of applications for membership from qualified clinical workers, less than 40 years of age, regardless of their specialty.

PROGRAM

Thursday, November 3, 1955

Thorne Hall, Northwestern University, Chicago, Illinois

Dr. Robert J. Glaser, Presiding

Presentations will be limited to ten minutes

9 a.m.

1. Application of Neutron Activation of Tissue to the Study of Muscle Electrolytes in Progressive Muscular Dystrophy and Other Muscular Disorders.

J. D. Williams, L. Reiffel,* B. M. Ansell,* C. A. Stone,* James A. Schoenberger and Robert M. Kark. Chicago, Illinois. page 204*

2. The Effect of Carbon Dioxide on the Concentration of Calcium in Ultrafiltrate of Serum Obtained by Centrifugation.

Ananda S. Prasad and Edmund B. Flink. Minneapolis, Minnesota. page 204*

3. Metabolic Aspects of Total Hypophysectomy in Advanced Breast Cancer.

Byrl J. Kennedy and William T. Peyton. Minneapolis, Minnesota. page 200*

4. Instances of Failure of High-Potency ACTH-Gel to Activate the Adrenal Cortex.

David H. P. Streeten, Holbrooke S. Seltzer, Manard E. Pont and Jerome W. Conn.* Ann Arbor, Michigan. page 201*

5. Spontaneous Hypoglycemia as a Manifestation of Early Diabetes Mellitus.

Holbrooke S. Seltzer, Stefan S. Fajans and Jerome W. Conn. Ann Arbor, Michigan. page 203*

6. Observations on the Use of 10% Glucose in the Early Treatment of Diabetic Acidosis.

Thomas B. Skillman, Margaret F. Kessler* and Harvey C. Knowles, Jr. Cincinnati, Ohio. page 203*

7. The Effect of Anesthesia on Intermediary Carbohydrate Metabolism.

William R. Drucker, Christine Costley,* Robert Stults,* Gilbert Gross,* William Holden,* Max Miller, James Craig and Hiram Woodward.* Cleveland, Ohio. page 202*

INTERMISSION (10 minutes)

8. The Effect of Tilting on the Right Atrial Pressures of Patients with Heart Failure.

B. M. Oser, J. R. Huston* and Joseph M. Ryan. Columbus, Ohio. page 197*

* By invitation

9. Right Intraventricular Block in Normal Subjects. *Sami Said* and J. Marion Bryant. New York, New York. page 196*

10. The Effect of Norepinephrine on the Electrolytes of Arterial Wall.

Louis Tobian, Jr. Minneapolis, Minnesota. page 199

11. Serum Transaminase Activity: Observations in a Large Group of Patients.

Murray Chinsky, George L. Shmagranoff* and Sol Sherry. Saint Louis, Missouri. page 200*

12. Blood Flow-Pressure Relationships During Unilateral Pulmonary Artery Occlusion with Special Reference to Congenital Heart Disease.

Bernard L. Brofman and Bernard L. Charms.* Cleveland, Ohio (introduced by Bennett Levine.) page 198*

13. The "Flush Technic" as an Aid in the Diagnosis of Coarctation of the Aorta in Infancy.

David Goldring, M. Remsen Behrer, Ernest E. McCoy,* Hulda Wohltmann* and Wilbur A. Thomas.* Saint Louis, Missouri. page 199*

14. The Syndrome of Acyanotic Tetralogy of Fallot: Clinical and Physiologic Studies of 6 Adult Cases.

Fouad Bashour and Paul Winchell, Minneapolis, Minnesota. page 198*

1:00 p.m.

LUNCHEON AND BUSINESS MEETING

Abbott Hall Dining Room

2:00 p.m.

15. A Morphologic Comparison of the Organisms Found in Isolated Lung Nodules of Histoplasmin Reactors with the Organisms Found in Acute Disseminated Histoplasmosis.

Martin A. Segal. Minneapolis, Minnesota (introduced by William W. Stead). page 208*

16. The Association of Histoplasmosis and Lymphoma.

Norman A. Nelson, Herbert L. Goodman and Harold L. Oster. Eloise, Michigan. page 208*

17. External Scintillation Counting over the Liver and Spleen after the Transfusion of Radioactive Erythrocytes.
Donald R. Korst, Dallas V. Clatanoff and Robert F. Schilling. Madison, Wisconsin.
page 195
18. The Relationship of Binding Power to Intrinsic Factor Activity.
Ronald C. Bishop, Milton Toporek and Frank H. Bethell.* Ann Arbor, Michigan.
page 194
19. Nonspherocytic Carriers of Hereditary Spherocytosis.
W. A. Newton, Jr. Columbus, Ohio.
page 195
20. The Effect of Intravenous Fat Emulsion on Total Bilirubin Output as a Measure of Hemolysis in Human Subjects.
John F. Mueller, Morton I. Grossman and Hugo C. Moeller. Denver, Colorado.
page 196
- INTERMISSION (10 minutes)
21. Some New Immunologic Studies on Purified Human Glomerular Basement Membrane and Dog Glomerular Basement Membrane in Vitro.
Raymond W. Steblay and Mark H. Lepper.* Chicago, Illinois.
page 211
22. Repair of Glomerular Lesions in Toxemia of Pregnancy.
Victor E. Pollak, Conrad L. Pirani,* Robert M. Kark, Robert C. Muehrcke, Vincent C. Freda* and John B. Nettles.** Chicago, Illinois.
page 209
23. The Effect of Mercurial Diuretics on Kidney Succinic Dehydrogenase.
*Robert G. Page and Daniel Porte, Jr.** Chicago, Illinois.
page 210
24. The Effect of Anemia and Polycythemia on Glomerular Filtration and Renal Vascular Tone.
James F. Schieve. Columbus, Ohio.
page 210
25. The Effect of Various Therapeutic Agents on the Gastric Hyperchlorhydria Induced by Intravenous Reserpine.
Mervin L. Clark and Edward M. Schneider. Oklahoma City, Oklahoma.
page 206
26. Studies on the Secretion of Pepsinogen, Acid and Water into Human Gastric Juice.
Basil I. Hirschowitz, John London and H. Marvin Pollard.* Ann Arbor, Michigan.
page 205

Officers of the Midwestern Section

CHAIRMAN

Robert J. Glaser, M.D.
St. Louis, Missouri

SECRETARY

William W. Stead, M.D.
Minneapolis, Minnesota

COUNCILLORS

Robert P. Gilbert, M.D.
Chicago, Illinois

James F. Hammarsten, M.D.
Oklahoma City, Oklahoma

Harper K. Hellems, M.D.
Detroit, Michigan

John F. Mueller, M.D.
Denver, Colorado

Advance Reports Submitted to the Annual Meeting of the Midwestern Section

of the
American Federation for Clinical Research
Thorne Hall, Chicago, Illinois • Thursday, November 3, 1955

BLOOD

Polycythemia of Obesity

By *Max H. Weil and Ananda S. Prasad*. University of Minnesota, Minneapolis.

A man weighing 380 pounds came under our observation in October 1953. He had a hemoglobin of 21.5 Gm. %, a hematocrit of 73% and certain metabolic abnormalities. These findings were completely reversed by weight reduction alone. At the end of 5 months he weighed 290 pounds and his hemoglobin had progressively fallen to 14.5 Gm. %, and the hematocrit to 44%. When last seen in November 1954, he weighed 226 pounds and was well. Normal hemoglobin and hematocrit values have persisted.

An increased incidence of polycythemia in obese patients was found on review of cases of obesity treated at University Hospital, Minneapolis, Minnesota. We were subsequently able to collect 4 additional cases of polycythemia related to obesity. These patients display decreased vital capacity, a decrease in arterial oxygen saturation, and elevation of the serum carbon dioxide content. Blood volume is high normal. Examination of the peripheral blood and bone marrow are noncontributory and do not help to distinguish this condition from polycythemia vera. Radioactive phosphorus (P^{32}) given to 2 patients diagnosed as polycythemia vera, before this entity was recognized, was ineffective. Three of 5 patients adhered to diet, and weight reduction was promptly followed by hemoglobin reduction.

In the very obese, the thoracic cavity is crowded by fat from within and without. The increased effort that is needed and the mechanical barrier that fat creates leads to inadequate pulmonary ventilation. Polycythemia is regarded by us as a consequence of hypoxia resulting from poor ventilation.

The Relationship of Binding Power to Intrinsic Factor Activity

By *Ronald C. Bishop, Milton Toporek and Frank H. Bethell*. Simpson Memorial Institute, University of Michigan, Ann Arbor.

The role of intrinsic factor in the absorption of vitamin B_{12} has long been under investigation. Some substances with intrinsic factor activity "bind" B_{12} and make it unavailable for growth in the microbiologic assay for the vitamin. The relationship of this binding power to intrinsic factor activity has not yet been definitely established. When pernicious anemia (PA) patients were used to evaluate the intrinsic factor activity of experimental preparations there was an incomplete correlation between such activity and the binding power of these preparations. One of the difficulties presented by the use of PA patients is that the gastric juice of such patients does have some binding power.

To circumvent the possible effect of the binding power of the PA patients' own gastric juice, the binding power-intrinsic factor relationship was studied in patients with total gastrectomies using the urinary excretion of orally administered radioactive $B_{12}Co^{60}$ as a measure of absorption. A control test, oral $B_{12}Co^{60}$ without intrinsic factor was followed by other tests at weekly intervals. In 1, an oral dose of $B_{12}Co^{60}$ was followed immediately by an oral dose of normal human gastric juice (GJ) which had been incubated for 30 min. at room temperature with equivalent amount of nonradioactive B_{12} . In the second part of the experiment, the $B_{12}Co^{60}$ was bound to GJ and the nonradioactive B_{12} was free. As a check on the effect of prolonged contact apart from binding, on absorption, a test was run with $B_{12}Co^{60}$ and GJ administered separately without prior incubation. The findings confirmed earlier observations that prior incubation does not enhance absorption.

The data indicate that the B_{12} already bound by GJ is preferentially absorbed. One series of tests on a PA patient gave similar results. It is concluded that binding power is necessary for intrinsic factor activity.

Some Observations on the Use of Cobaltous Chloride in Hypoplasia of the Marrow and Refractory Megaloblastic Anemias

By Robert J. Rohn and William H. Bond. Department of Medicine, Indiana University School of Medicine, Indianapolis. (Aided in part by a grant from Lloyd Brothers, Inc.)

The mechanism whereby cobaltous chloride induced polycythemia is poorly understood. It has been postulated by some investigators that this agent directly increases hematopoiesis, and some observations suggest that all elements of the marrow might be stimulated.

To study the effect of this agent in various hypoplastic states cobaltous chloride was accordingly administered to the following groups of patients: idiopathic hypoplasia of the marrow, 5; hypoplasia of the marrow secondary to chronic renal failure, 2; hypoplasia of the marrow secondary to acute monocytic leukemia, 1; refractory megaloblastic anemia, 4.

These patients varied in age from 23 mo. to 81 yr. The minimal dosage of cobaltous chloride was 90 mg./day, and the maximal administered dosage was 300 mg./day. Except for 1 patient who received cobaltous chloride for only 9 days, the drug was administered for 21 to 56 days. All these patients experienced varying degrees of gastrointestinal distress.

Of the 12 patients studied, only 2 patients demonstrated any significant hematologic improvement while cobaltous chloride was being administered. One of these patients subsequently developed leukemia, and the other was lost to observation. The blood picture was completely unchanged in the other 10 patients.

Nonspherocytic Carriers of Hereditary Spherocytosis

By W. A. Newton, Jr. Departments of Pathology and Pediatrics, The Ohio State University, Children's Hospital, Columbus.

The parents of 5 children with Coomb's negative chronic hemolytic anemia characterized by reticulocytosis, hyperbilirubinemia, spherocytosis increased osmotic erythrocyte fragility and shortened red cell survival were studied by the usual tests and found to show no significant hematologic abnormality. This study included erythrocyte osmotic fragility determination after 24 hr. sterile incubation.

Since the clinical and hematologic pictures of these children was so strikingly suggestive of hereditary spherocytosis, the erythrocytes of both parents were studied by the Ashby red cell survival technic. By this method 1 parent in each family showed a significant shortening of red cell survival, while the other parent showed no decrease in red cell survival.

Four of these children have been splenectomized, with a sustaining complete hematologic remission. The 5th child has not yet been treated.

Nearly all recent reports of the pattern of in-

heritance of hereditary spherocytosis have described a few families in which no abnormalities were detected in either parent of a patient with the typical syndrome. Various explanations such as mutation, incomplete penetrance, acquired nature of the disease and illegitimacy have been suggested.

This study suggests that the parent showing a functional defect of erythrocytes demonstrated by the survival technic has a form of this syndrome which can be detected only by this method. Inheritance, then, seems to follow the classic pattern of mendelian dominance in these cases.

This method of study of the parents seems indicated when no obvious defect is present in the parents of a child with this syndrome.

External Scintillation Counting over the Liver and Spleen after the Transfusion of Radioactive Erythrocytes

By Donald R. Korst, Dallas V. Clatanoff and Robert F. Schilling. Department of Medicine, University of Wisconsin, Madison.

Studies by others have demonstrated that the "normal" spleen of patients with idiopathic thrombocytopenia will trap the spherocytic erythrocytes transfused from a donor with hereditary spherocytosis (HS). In the present study spherocytes were labeled with radiochromate and divided into 2 aliquots: 1 was reinjected into the donor (HS), who had splenomegaly, and the other was transfused into a normal recipient (N). Survival of these spherocytes was markedly shortened and very similar in the 2 recipients. External scintillation counting revealed a spleen to liver radioactivity ratio of 4:1 in each subject. The same 2 individuals were next studied in the reverse fashion, i.e., each received radioactive normal erythrocytes from the normal donor (N). Survival of these cells was normal in each recipient. The ratio of splenic radioactivity to hepatic radioactivity was 0:9 in the normal and 1:9 in the HS patient, who had a large spleen.

Having demonstrated in the model system of HS that the spleen will show a much higher radioactivity than the liver when the spleen is "trapping" radioactive erythrocytes, studies were next made on 5 patients with acquired hemolytic anemia. Two such patients having splenic to hepatic radioactivity ratios of 3:5 and 4:3 were splenectomized, and there ensued a striking amelioration of the hemolytic process in each. In 1 of these patients the radioactivity of splenic pulp erythrocytes was 10 times that of erythrocytes from a peripheral vein.

One patient with a severe hemolytic process and a splenic to hepatic radioactivity ratio of 1:7 had no discernible benefit from splenectomy. The other two patients, who were not splenectomized, had radioactivity ratios of 3:5 and 1:2.

The data clearly indicate that there are two types of acquired hemolytic anemia, as regards

splenic "trapping" of erythrocytes. The spleen in some patients with acquired hemolytic anemia is a much more active trap of erythrocytes than it is in other patients. The few observations it has been possible to make suggest that patients showing evidence of active splenic "trapping" of erythrocytes are more likely to benefit from splenectomy than are those lacking this evidence.

The Effect of Intravenous Fat Emulsion on Total Bilirubin Output as a Measure of Hemolysis in Human Subjects

By *John F. Mueller, Morton I. Grossman and Hugo C. Moeller*. Medical Nutrition Laboratory, Fitzsimons Army Hospital, Denver, Colorado.

Fever is a common complication of parenteral fat alimentation. Among the many theories as to the cause of the thermogenic response, the occurrence of intravascular hemolysis has been prominently suggested. Anemia has been found in laboratory animals given intravenous fat over long periods of time. Hemoglobinemia is frequently seen in lipemic plasma. It has been suggested that the former is a consequence of the known marked increase in mechanical fragility of red cells in the presence of fat. There are conflicting reports in the literature on studies in humans. Three patients were studied by Creditor, 2 of whom had slightly elevated fecal urobilinogens after 1 fat infusion. Shafiroff found no elevation of the urinary urobilinogen after fat.

As previously reported from this laboratory, bile collected via a biliary fistula in intact rabbits showed no increase in bilirubin content after the injection of 10 ml./Kg. of a 10% fat emulsion. Subsequent studies in rats utilizing a similar technic have revealed elevated values for bilirubin after 40 ml./Kg. and 20 ml./Kg. injections of fat as compared to those before. However, with 10 ml./Kg. dose no increase occurs.

It seemed advisable to resolve this problem in human beings. Therefore, analyses of total bilirubin output in bile collected from 7 patients via an in-

dwelling T-tube in their common duct following gall-bladder surgery were carried out before and after one 600 cc. fat infusion. Collections were continuous for 48 hours before and 48 hours after the infusion. The results indicate that there is no increase in the output of bilirubin in human subjects following the parenteral administration of fat, and that in the dosage level used hemolysis could not be demonstrated *in vivo*. Febrile responses occurred in 2 of the patients, indicating that mechanisms other than hemolysis were responsible.

Clinical Evaluation of Sinthrom (G-23350), a New Oral Anticoagulant

By *J. A. Polhemus, W. S. Wilson, P. W. Willis III, J. R. Gamble, D. R. Griffith, P. E. Hodgson and I. F. Duff*. Ann Arbor, Michigan.

Sinthrom (nitrophenyl acetyl-ethyl-4-oxycoumarin) was given orally to 56 patients, 40 of whom had normal pretreatment prothrombin values (80% or above, Quick method). The results were compared with those obtained in other individuals treated with Dipaxin, Dicumarol, Phenylindandione and Tromexan.

The aim of therapy was to maintain prothrombin concentration between 20 and 30% of normal. The usual initial dose of Sinthrom was 28-32 mg. followed by 16-24 mg. on the 2nd day. The average daily maintenance dose was 6-16 mg. and the maintenance dose was found to vary greatly in the same patient from day to day. A single daily dose was usually employed, since no difference was noted when the drug was given twice daily. No absolute resistance to Sinthrom was encountered. The excessive effect of Sinthrom was rapidly reversed by oral or intravenous Vitamin K₁. Bleeding, usually mild epistaxis or hematuria, occurred in 12% of the patients. Pre- and post-treatment renal and liver function studies were performed in 2 patients and no abnormalities were noted. Though Sinthrom is the most potent of the oral anticoagulants evaluated by this group, the dosage was found difficult to regulate.

CARDIOVASCULAR SYSTEM

Selective Phonocardiography

By *C. Aravanis, L. Richmond and A. A. Luisada*. Chicago Medical School, Chicago.

Eight normal subjects and 30 clinical cases were studied by means of a variable band pass filter with additional amplification. The various frequencies of the cardiac murmurs were analyzed. A band between 60 and 110 vibrations/sec. was found adequate for magnifying and recording murmurs caused by mitral defects. A band between 150 and 200 was

found adequate for magnifying and recording murmurs caused by aortic insufficiency.

A routine method of study of cardiac murmurs, called "selective phonocardiography," is outlined. It is based on the use of the 2 above bands, in addition to "stethoscopic" phonocardiograms.

Right Intraventricular Block in Normal Subjects

By *Sami Said and J. Marion Bryant*. Fourth Medical (N.Y.U.) Division, Bellevue Hospital,

and the Department of Medicine, New York University Post-Graduate Medical School, New York City.

The presence of secondary R waves in leads from the right side of the chest with QRS durations of less than 0.12 sec. has been considered in recent electrocardiographic literature as representing incomplete right bundle branch block or other forms of intraventricular block. The significance of this entity has not been adequately evaluated. Its appearance has been associated by many authors with various forms of heart disease, and only by a few with normal hearts.

The present study is based on the findings in a series of young adults without heart disease. Electrocardiographic leads were recorded from multiple sites on the chest and from the esophagus. Simultaneous monitor leads were used as reference points in timing the various QRS deflections. Secondary R waves in 1 or more of these leads were observed in the great majority of the subjects examined. In most cases these secondary R waves, thought to represent late activation of the right ventricle, were present in high or conventional anterior chest leads. A small minority showed such deflections only in lateral or posterior chest leads.

Secondary R waves were present in V_R in about one-half of all cases. The QRS duration varied from 0.08 to 0.12 sec. with the greater number nearer the former value.

Therefore, it is concluded that the presence of secondary R waves in leads opposite the right ventricle is the rule rather than the exception in normal young adults. Also, the concept of "incomplete right bundle branch block" is questioned and a revision of nomenclature is thought to be in order.

The Blood Pressure Effect of Rauwolfia serpentina and Reserpin in Essential Hypertension: A Long-Term Double Blind Study

By Murray B. Sheldon, Robert Helm, J. Harold Kotte, William Stiles, Isom C. Walker and James Evans. Department of Medicine, University of Cincinnati College of Medicine, Cincinnati, Ohio.

A total of 15 patients with benign essential hypertension were treated in a conventional double blind study over a period of 22 months, during which time they received either Rauwolfia serpentina (50 mg., 4 times daily), Reserpin (.25 mg., 4 times daily) or an identical placebo for alternate periods of 6 to 12 weeks. All patients were observed for a variable period of time during which they received no medication or placebo.

During the entire period blood pressures were checked in the supine, seated and standing positions. A random selection of patients was also followed independently in group psychotherapy. Blood pressure readings were subjected to statistic analysis by the method of analysis of variance.

The results indicated that there was a statistically significant effect of the drugs over the placebo and no medication: in the systolic blood pressure in 6 patients and in the diastolic blood pressure in 8 patients. This effect was highly significant in 4 and 6 patients on the systolic and diastolic pressures respectively. One patient had a highly significant blood pressure response to the placebo as compared to no therapy. One patient had a significantly poor response to the drug as compared to the placebo or no therapy. There was no instances in which there appeared to be a significant postural blood pressure effect during any of the observed periods.

The Effect of Tilting on the Right Atrial Pressures of Patients with Heart Failure

By B. M. Oser, J. R. Huston and J. M. Ryan. Department of Medicine, Ohio State University College of Medicine, Columbus.

The effect of upright tilting on right atrial pressure was determined in 24 patients with heart disease of various types. Seven had no failure, the rest had moderate to advanced failure. Ten controls included 7 normals and 3 with massive noncardiac edema.

Supine, a point half the distance from the front to the back of the chest at the 4th right intercostal space was our reference. Upright, the catheter tip in the mid-right atrium (fluoroscopically) was the reference. Pressures were determined in mm. H_2O with a water manometer.

Subjects, with and without heart disease and also with and without edema, having a recumbent pressure of 100 or less had an average pressure drop of 81 when upright. Those with recumbent pressures between 100 and 200 had an average drop of 94, while those with recumbent pressures greater than 200 had an average drop of 166 when tilted. When these high pressures approached normal following treatment, the response to tilt also approached normal. A direct correlation exists between the height of the recumbent pressure and the fall of this pressure after tilting ($r = .768$).

It appears that in advanced congestive failure the vascular bed remains distensible. When upright, the increased venous hydrostatic pressure below the diaphragm may exceed venous tone and result in blood trapping, thus reducing right atrial pressure. The effect is probably similar on pulmonary venous pressure. Since elevated pulmonary venous pressure may be a respiratory stimulus, an orthostatic reduction in this pressure would help explain orthopnea and also the relief of paroxysmal nocturnal dyspnea. The characteristics of a venous pressure-volume diagram may partially explain why the highest recumbent pressures have the greatest drops after tilt. The orthostatic decrease in intrathoracic pressure probably accounts for only a small portion of the atrial pressure change.

Simultaneous Estimations of Intravascular Volumes in Congestive Heart Failure with Tagged Erythrocytes and Tagged Human Serum Albumin. The Effect of TEAC on Intravascular Volume and Venous Pressure.

By *J. A. Moorhouse, A. P. Remenik and R. M. Kark*. The Department of Medicine, Presbyterian Hospital and the Department of Medicine, Research and Educational Hospitals, University of Illinois College of Medicine, Chicago.

Thirteen patients with congestive heart failure have been studied. In 12 treatment was successful. Intravascular volume was measured before and after therapy by P^{32} -tagged human erythrocytes and I^{131} -tagged human serum albumin. The cell suspension and albumin solution were mixed immediately prior to injection. Serial venous blood samples were taken over a 45-minute period. After withdrawal of a sufficient number of samples to establish the regression lines, tetraethyl ammonium chloride (TEAC) was injected intravenously. Further sampling was done to determine the variation in volume induced by this agent. Continuous measurements of venous pressure were taken throughout the procedure. The P^{32} and I^{131} content of each whole blood sample was determined by differential counting of beta and gamma radiation.

The intravascular volumes as determined by I^{131} albumin exceeded the determinations by P^{32} -tagged erythrocytes by a mean of 0.65 L., 15.6% ($p = 0.001$) before treatment; 0.71 L., 19.8% ($p = 0.001$) after treatment. The I^{131} volumes before treatment exceeded those after treatment by a mean of 0.44 L. ($p = 0.06$). The P^{32} volumes before treatment exceeded those after treatment by a mean of 0.52 L. ($p = 0.01$). Following injection of TEAC in the pretherapy studies, there occurred a mean increase in the I^{131} volume of 7.1% ($p = 0.05$); in the P^{32} volume of 4.6% ($p = 0.3$). In 9 cases TEAC induced a fall in venous pressure of from 4 to 7.5 cm. An incidental finding was the fall in hematocrit associated with venipuncture and serial blood sampling. Hematocrits fell from 2 to 9% of their initial value over a 45-minute period.

Blood Flow-Pressure Relationships During Unilateral Pulmonary Artery Occlusion with Special Reference to Congenital Heart Disease

By *Bernard L. Brofman and Bernard L. Charms*. Mount Sinai Hospital, Cleveland, Ohio. (Aided by a grant from the Cleveland Area Heart Society.)

More than 60 cardiac catheterizations have been carried out with a triple lumen balloon-tipped catheter, by means of which the right or left main pulmonary artery may be occluded under fluoroscopic control. This procedure has been carried out without untoward effects in a series of controls and

in patients with various types of cardiac and pulmonary diseases. Significant alterations in pulmonary blood flow-pressure relationships have been demonstrated. However, there does not appear to be an obligate relationship between control pulmonary artery pressure and the pressure response to unilateral occlusion. Studies in patients with increased pulmonary artery blood flow (hyperthyroids, congenital left-to-right shunts) attest to the tremendous adaptability of the normal lung. By the same token, in patients with fixed pulmonary resistance sudden diversion of total blood flow through one lung is attended by a marked pulmonary artery pressure rise. In no case did unilateral pulmonary artery occlusion cause the alarming manifestations of acute cor pulmonale.

Observations during the study of patients with congenital heart disease are of particular interest. In one patient with a patent ductus arteriosus and normal pulmonary artery pressure, unilateral pulmonary artery occlusion produced a moderate rise in main pulmonary artery pressure and an equivalent decrease in shunt flow. In another patient, with undiagnosed congenital heart disease, in whom no murmur could be heard, the control pulmonary artery pressure was found to be equal to femoral arterial pressure. No shunt could be demonstrated. When unilateral pulmonary artery occlusion produced only a slight further rise in main pulmonary artery pressure, simultaneous brachial and femoral arterial blood samples revealed an abrupt decrease of femoral arterial oxygen content with no change in brachial arterial content. This demonstrated a reversal of flow through a hitherto unsuspected patent ductus arteriosus, which diagnosis was confirmed at operation. This technic has also been applied in attempting to differentiate abnormal drainage of pulmonary veins from atrial septal defects.

The Syndrome of Acyanotic Tetralogy of Fallot: Clinical and Physiologic Studies of Six Adult Cases

By *Fouad Bashour and Paul Winchell*. University of Minnesota, Minneapolis.

Infrequently, noncyanotic patients with the anatomic features of tetralogy of Fallot have been described.

In 6 adult patients studied, the findings of pulmonary stenosis, ventricular septal defect and a preponderant left to right shunt through the defect have been established by cardiac catheterization. In 1 patient, marked peripheral arterial cyanosis developed after exercise.

Clinically, all patients had normal body development, led active lives with certain restrictions imposed by the appearance of cyanosis upon exertion. Squatting was absent in all of them. Clubbing of the fingers and toes was present in 3 out of 6. A systolic thrill at 3rd left IS was felt in 4 out of 6,

and a systolic murmur in all of them was discovered early in life. The electrocardiogram revealed a right ventricular preponderance with a sinus rhythm. On radiography, right ventricular enlargement, prominent pulmonary artery segment and normal lung vasculature were present in all. In only 1 patient was pulmonary stenosis of the valvular type.

In 1 patient, surgical repair of the defect and excision of the stenotic valve were attempted. In 2 patients, resection of the stenotic area was attempted, followed by death of 1 and no significant improvement in the other.

The most important factor influencing the direction of flow through the defect is the severity of the pulmonary stenosis. The presence of relatively mild pulmonary stenosis seems to be protective to the pulmonary vasculature, and may prevent development of pulmonary hypertension. This may be one of the mechanisms allowing prolonged survival in some patients with tetralogy of Fallot reaching advanced age.

The "Flush Technic" as an Aid in the Diagnosis of Coarctation of the Aorta in Infancy

By *David Goldring, M. Remsen Behrer, Ernest E. McCoy, Hulda Wohltmann and Wilbur A. Thomas.*
Washington University School of Medicine, St. Louis, Missouri.

Coarctation of the aorta in infancy is seen with enough frequency in an active pediatric hospital service to warrant a report of our experiences. Sixteen cases of coarctation of the aorta in infants have been admitted and studied at the St. Louis Children's Hospital since 1950. All patients in this series died and the diagnosis verified by autopsy.

Blood pressure studies were performed on each patient by using the "flush technic," which is carried out by placing a blood pressure cuff around the wrist or ankle and blanching the extremity. The cuff is then inflated and the pressure slowly released until the extremity flushes. The approximate systolic pressure is read at the first appearance of this flush. The blood pressure studies revealed a gradient of at least 20 mm. Hg between the arms and legs in most instances, but in several patients hypotension was present in all extremities.

The Effect of Norepinephrine on the Electrolytes of Arterial Wall

By *Louis Tobian.* Department of Medicine, University of Minnesota School of Medicine, Minneapolis.

Fourteen nembutalized dogs were infused for 30 min. with enough norepinephrine to keep mean arterial pressure 100 mm. Hg above preinfusion levels. Five control dogs were treated identically except that the saline infusion did not contain norepinephrine. A sample of one femoral artery was

obtained from each dog before the infusion, the other femoral was obtained during the last 5 minutes of the infusion.

Norepinephrine produced a striking, highly significant fall in the potassium content of the arteries, the decrease varying from 4 to 59% (av. 27%). The saline controls showed an average increase of 17% in artery potassium content. Norepinephrine also produced a significant increase in artery sodium content, an average gain of 1.7 mEq./100 Gm. of solids while the saline controls were losing 0.4 mEq. of sodium. The mEq. gain in sodium after norepinephrine averaged only $\frac{3}{4}$ the loss of potassium. However, in individual dogs, sodium and potassium seemed to change independently. In 6 dogs there was virtually no gain in sodium to replace the considerable loss of artery potassium. In 4 other dogs the sodium increase significantly exceeded the potassium loss. Forty-five minutes after the end of the norepinephrine infusion, the artery had regained the potassium lost during the infusion. The changes in chloride content of artery and of serum, a measure of extracellular water, were not significantly different in the norepinephrine group compared to the saline control group.

The data suggest that potassium content of arterial smooth muscle is largely independent of a "sodium pump" mechanism. The loss of artery potassium with norepinephrine is probably intimately linked with the contraction of arterial muscle produced by norepinephrine. The pattern of electrolyte alteration in arteries after norepinephrine is different from the abnormal pattern characteristic of renal hypertension.

Intravascular Bentyt: Effects upon Peripheral Circulation

By *Donald C. Ausman and Robert R. Ausman.*
The Ausman Clinic, Milwaukee, Wisconsin.

Changes in skin temperature were recorded and used as an index of improved peripheral circulation in 9 patients suffering from arteriosclerosis obliterans and treated with parenteral Bentyt hydrochloride. In 8 of the 9 patients, clinical improvement with healing of leg ulcers was associated with treatment. In a series of 61 injections (44 into the femoral artery; 17 into the antecubital vein), the individual dose varied from 20 mg. to 50 mg. The greatest increase in temperature (11.5°F. in one case) was recorded from the great toe. There was no difference in the response to intra-arterial Bentyt and intravenous Bentyt; increases in temperature were similar in both extremities. The immediate response in 29 of the intra-arterial and in 7 of the intravenous injections was a slight, transient decline. The maximal increase in skin temperature occurred at variable times, usually 40 to 60 min. after injection.

In 15 instances, a posterior tibial nerve block with 1% procaine was employed (7 with Bentyt; 8

without Benty). Of the 8 without Benty, 4 showed an initial transient temperature decline. The increase in temperature was first seen in the blocked leg, but sometimes the greatest increase occurred in the other leg. The 7 blocks immediately preceded by or followed by Benty failed to produce a further temperature rise.

The Effect of Buerger's Exercises on the Oxygen Tension of the Skin of Limbs Having Severe Occlusive Arterial Disease

By *Raymond Penneys and David S. Wiltsie*. Vascular Section, Robinette Foundation, Hospital of the University of Pennsylvania, Philadelphia.

Oxygen tension was measured by the stationary platinum electrode of Davies and Brink. Several electrodes were inserted in the skin at the base of the toes on the dorsum of the foot. The exercise cycle consisted of a 3-min. period while the subject sat with feet dependent over the side of a bed, and a 3-min. period of recumbency. This cycle was repeated 2-4 times. Thirteen experiments were performed on 10 patients having severe peripheral arterial occlusive disease, and 4 experiments were carried out on 4 normal subjects. In both groups of subjects the mean oxygen tension was found to be approximately 70% greater when the feet were dependent, than when the subject was horizontal. Little additional increment was gained in successive cycles. The final oxygen tension, in the horizontal position, was essentially the same as that just before the exercises were begun.

This increase in skin oxygen in the dependent position indicates that Buerger's exercises are of value in the treatment of peripheral arterial disease.

Serum Transaminase Activity: Observations in a Large Group of Patients

By *Murray Chinsky, George L. Shmagranoff and Sol Sherry*. Division of Medical Services, Jewish Hospital of St. Louis, and the Department of

Medicine, Washington University School of Medicine, St. Louis, Missouri.

Recent studies have demonstrated the presence of glutamic oxalacetic transaminase in normal human sera, and its significant elevation in diseases associated with myocardial and hepatic necrosis. To evaluate the usefulness of serum transaminase assays as a diagnostic procedure, the serum transaminase activity of normal adults, and of 400 patients with varied diseases was determined.

Serum transaminase activity of normal adults ranged from 7 to 40 U/ml. of serum with an average of 20 ± 8 U/ml. The serum transaminase activity was independent of time of day, relation to meals, and previous exercise. Bile was observed as a significant normal route of excretion for this enzyme.

Of a group of 117 diagnosed myocardial infarctions, 108 or 92% were associated with an abnormally high serum transaminase. When specimens were taken at proper intervals, only 1 case of the entire group failed to develop an abnormally high value. The peak transaminase activity was observed 24 hours after onset of pain. Evidence was obtained that the appearance of very high transaminase levels (above 200 U) may be a poor prognostic sign. The serum transaminase remained in the normal or borderline range in 69 patients with the anginal syndrome. In 12 of these latter patients, the occurrence of significant, though not elevated, serial changes in transaminase activity suggested the presence of subclinical infarcts.

Elevated serum transaminase levels were observed in patients with hepatic necrosis as well as the majority of patients with obstructive and other types of jaundice, acute pancreatitis and very rapid cardiac arrhythmias. Normal levels were observed in a variety of inflammatory, infectious, neoplastic, degenerative and metabolic diseases.

At the present state of knowledge the serum transaminase assay, when carried out at the appropriate time, is most useful in excluding significant myocardial or hepatic necrosis.

ENDOCRINES AND METABOLISM

Metabolic Aspects of Total Hypophysectomy in Advanced Breast Cancer

By *B. J. Kennedy and William T. Peyton*. Departments of Medicine and Surgery, University of Minnesota Medical School, Minneapolis.

Alterations of the hormonal status of an individual may profoundly influence the course of advanced breast cancer. The maintenance and growth of the cancer is dependent upon hormonal factors of the ovaries, adrenal glands and pituitary gland. Earlier observations on the response of ad-

vanced breast cancer to hormonal alterations have provided a physiologic basis for total hypophysectomy.

Seventeen patients with metastatic breast carcinoma have had a surgical hypophysectomy. Nine of these have demonstrated striking objective regressions of metastatic lesions for periods up to 19 months postoperatively.

Metabolic balance studies support the clinical observations in demonstrating an increase in serum alkaline phosphatase, decrease in serum calcium, decrease in hypercalcuria and a positive calcium

balance. Endocrine studies demonstrated a decrease in thyroid and adrenal function. Polyuria and polydipsia have occurred in some patients.

Hypophysectomy in selected patients offers another means of producing an alteration of hormonal balance with improvement in the disease.

Tryptophan Metabolism in Patients with Neoplastic Disease

By *J. M. Price, R. R. Brown, A. R. Curreri and Forde A. McIver*. Cancer Research Hospital, University of Wisconsin Medical School, Madison.

The urinary excretion of several metabolites of tryptophan has been determined for patients with and without neoplastic disease before and after oral administration of 2 Gm. of L-tryptophan. The patients were maintained on a general hospital diet and were kept on a clinical research ward. Two 24-hour urine specimens were collected before, and 3 were collected after the administration of a single dose of the amino acid. The urine samples were analyzed quantitatively for several tryptophan metabolites including kynurenine, acetylkynurenine, anthranilic acid, o-aminohippuric acid, anthranilic acid glucuronide, kynurenic acid, xanthurenic acid and N-methyl-2-pyridone-5-carboxamide.

The control subjects consisted of several healthy laboratory workers and a number of patients who had been hospitalized for minor surgery or a variety of medical problems. The patients with neoplasms had primary malignancies of the breast, lung, kidney, ovary or fibrous connective tissues, as well as isolated examples of other primary sites of involvement.

About half of the patients with tumors excreted amounts of the various metabolites that were in the same range as the control subjects. The remaining subjects with cancer excreted larger quantities of kynurenine, acetylkynurenine and kynurenic acid than the controls, but only after the test dose of tryptophan.

No type of tumor was invariably associated with an abnormal pattern of excretion of metabolites in response to the tryptophan. However, most patients with fibrosarcoma or carcinoma of the breast had abnormal levels of urinary kynurenine, acetylkynurenine and kynurenic acid. One patient studied before and after surgical excision of a large fibrosarcoma had an abnormal pattern before, but not after surgery.

Instances of Failure of High-Potency ACTH-Gel to Activate the Adrenal Cortex

By *David H. Streeten, D. Phil, Holbrook S. Seltzer, Manard E. Pont and Jerome W. Conn*. Division of Endocrinology and Metabolism, Department of Internal Medicine, University Hospital, Ann Arbor, Michigan.

Lack of adrenocortical responsiveness to an 8-hour intravenous infusion of ACTH has proved to

be the most reliable criterion of adrenal insufficiency. When the new high-potency preparations of ACTH-gel became available, the convenience of their administration once or twice daily by intramuscular injection insured their immediate and widespread use, both for diagnostic and therapeutic purposes. To date, use of these preparations has been very successful, and no instances of inactivation of the hormone, with consequent failure of the adrenal response, have been reported.

During the past year we observed 8 instances of failure to respond to intramuscularly administered high-potency ACTH-gel, in individuals who had received no ACTH previously. All exhibited normal responses to intravenously administered ACTH. These individuals include: (1) 3 patients in whom the diagnosis of Addison's disease had been made because of subnormal or absent eosinophil and/or 17-ketosteroid responses to ACTH-gel (40 clinical U/12 hr.). One of these patients had been treated for adrenal insufficiency for several months without improvement before an intravenous ACTH test revealed normal eosinopenic and 17-hydroxycorticoid responses. (2) One patient received a therapeutic course of ACTH-gel (40 clinical U/12 hr.) without clinical improvement, and with no 17-ketosteroid response. Again there was a good response to intravenous ACTH. (3) Four out of 5 normal male medical students tested showed subnormal responses to 40 clinical U of ACTH-gel every 12 hours. Increasing the dose to 50 or 80 U twice daily improved performance of the adrenal but not invariably.

These observations indicate the necessity of performing intravenous ACTH tests on all patients who show an inadequate response to the diagnostic test with intramuscular ACTH-gel. If the clinical response to therapeutic administration of the gel is poor, and urinary ketosteroids reveal an inadequate rise, treatment should be changed to intravenous ACTH or hydrocortisone.

The Effects of Intermittent Administration of ACTH on the Adrenal Cortical Responsiveness of Patients on Prolonged Corticoid Therapy

By *Irving I. Young, Vito DeFilippa, Frank L. Meyer and William Q. Wolfson*. Unit for Metabolic Research, Department of Medicine, Wayne University College of Medicine and City of Detroit Receiving Hospital, Detroit, Michigan.

Adrenocortical unresponsiveness to exogenous ACTH is frequently but not invariably demonstrable in patients receiving therapeutic doses of adrenal steroid for prolonged periods. The hypofunction of the pituitary-adrenal axis induced by sustained high blood corticoid levels has been responsible for a number of episodes of adrenocortical insufficiency and death in the face of stress. On the other hand, while administration of ACTH also temporarily suppresses anterior pituitary production of ACTH,

it maintains the adrenal cortex in a hyperplastic state and probably enables the organism to cope with a stressful situation more adequately.

Adrenocortical response to intermittent administration of ACTH-gel at weekly intervals has been studied in a group of patients on long-term corticoid therapy to evaluate the ability of ACTH to maintain adrenal responsiveness. Subjects were initially tested to establish the state of their adrenocortical responsiveness and were then placed on a combined program of hydrocortisone, cortisone or Prednisone 5 or 6 days a week, and ACTH-gel in doses ranging from 100 to 320 U on each 7th day. The weekly corticotropin conveniently served as a test dose to evaluate adrenal function periodically. Periods of therapy ranged from 4 to 22 weeks. Each subject was at some subsequent period of time treated with adrenal steroids alone, to establish the adrenal suppressive effect of approximately equivalent doses.

One hundred units of ACTH-gel per week in combination with steroid therapy failed to prevent the development of adrenal unresponsiveness in 3 instances and produced demonstrable but definitely subnormal responsiveness in 1 other. Two hundred to 320 U/week were found to be adequate in 4 of 5 trials as measured by the fall in total eosinophil count 8 hours after the test dose of ACTH-gel, and the rise in urinary 17-hydroxycorticoids during the 24 hours following ACTH. Subjects with corticoid induced adrenal cortical unresponsiveness prior to initiation of the combined therapy were found to have demonstrable but subnormal responsiveness in 2 of 3 trials.

Adrenocortical atrophy may in most instances be prevented in individuals with previously normal adrenocortical function by large weekly doses of ACTH-gel.

Ketogenic Steroids as Determined by the Sodium Bismuthate Oxidation Procedure

By Donald J. Rohrsen and James T. Bradbury.
Department of Obstetrics and Gynecology,
University Hospitals, Iowa City, Iowa.

Norymberski and coworkers have published a series of studies which show that glucocorticoids can be oxidized to 17-ketosteroids. The quantitative estimation of ketogenic compounds is advocated as an index of the adrenal production of glucocorticoids. Sodium bismuthate is used as the oxidizing agent, and the method is relatively simple.

We have used the Norymberski method on known steroid compounds and on urines from a series of patients in an effort to judge its clinical value. We have confirmed his finding that normal individuals excrete from 4 to 6 mg. of ketogenic material per day. A 21-year-old girl with the adrenogenital syndrome receiving 100 mg. of cortisone orally/day was found to be excreting 4.5 mg. of pre-

formed 17-ketosteroids/day as compared to 25 mg. of ketogenic steroids. This indicated a 25% recovery of the administered cortisone. A 4-year-old girl with congenital adrenal virilism was excreting 35 mg. of 17-ketosteroids and 39 mg. of ketogenic steroids/day. Cortisone was then administered (50 mg. i.m./day). The ketosteroid excretion fell to 4.0 mg./day and the ketogenic value fell to 16.5 mg./day. A 26-year-old male with adrenal virilism excreted 40 to 60 mg. of ketosteroids/day and 60 to 80 mg. of ketogenic steroids/day. His steroid responses to cortisone and ACTH are being studied.

Bongiovani et al. (1952) have postulated that the primary etiology of the adrenogenital syndrome is an inability of the adrenals to produce glucocorticoids. The high ketogenic values in cases of adrenogenital syndrome indicate that 17-OH progesterone and/or pregnanetriol are the substances being oxidized. This detracts from the value of the sodium bismuthate method as a measure of the production of glucocorticoids.

The Effect of Anesthesia on Intermediary Carbohydrate Metabolism

By William R. Drucker, Christine Costley, Robert Stults, Gilbert Gross, William Holden, Max Miller, James Craig and Hiram Woodward. Departments of Surgery and Medicine, Western Reserve University, Cleveland, and Highland View Hospital, Cleveland, Ohio.

Previous studies of carbohydrate metabolism have revealed that glucose tolerance is decreased whereas fructose tolerance is unchanged after various stresses (surgery, infection, starvation). These changes are similar to those found in diabetes mellitus and have been interpreted as due to blocks of specific enzymatic processes in intermediary carbohydrate metabolism. Since it is known that glucose metabolism may be altered by certain anesthetic agents, the question arises whether anesthesia also alters carbohydrate metabolism by blocking specific enzymatic activity or whether anesthesia might act as a general enzymatic inhibitor and thereby interfere with the metabolism of fructose as well as glucose.

Patients were studied by a series of 3 daily glucose or fructose tolerance tests: one test before, one during anesthesia (without surgery), and one after anesthesia (Pentothal, Pentothal-oxygen-ether or drop ether). The results indicate that no consistent alterations occurred in either glucose or fructose tolerance with Pentothal. In contrast to the results with Pentothal, a decrease in glucose tolerance occurred whenever ether was used, either alone or with Pentothal. Relatively little alteration was found in fructose tolerance with ether. These results are interpreted as indicating that, under the conditions studied, ether decreases glucose tolerance in some different manner from a general enzymatic

inhibitor. Serum inorganic phosphate usually rose during ether anesthesia, a finding different from that seen with tolerance tests after other stresses.

Spontaneous Hypoglycemia as a Manifestation of Early Diabetes Mellitus

By *Holbrooke S. Seltzer, Stefan S. Fajans and Jerome W. Conn*. Division of Endocrinology and Metabolism, Department of Internal Medicine, University Hospital, Ann Arbor, Michigan.

A large number of patients with early, mild and unrecognized diabetes mellitus suffer from symptomatic and demonstrable spontaneous hypoglycemia. Such symptoms represented the chief complaint in 54% of 87 patients in whom this syndrome has been demonstrated. The hypoglycemia is of the "stimulative" type, occurring 3 to 5 hr. after meals. This may be one of the earliest clinical manifestations of diabetes mellitus.

Eighty-seven instances of this phenomenon have been observed during the past 5 years. Glucose tolerance tests after standard dietary preparation are clearly diagnostic of diabetes mellitus, but a precipitous hypoglycemia occurs between the 3rd and 5th hr. In this series the low level ranged from 25 to 50 mg. %. There was no clinical or laboratory evidence of hepatic impairment or other significant disease.

Forty-one of these patients had a definite or presumptively positive family history of diabetes. Twenty-four presented the combination of symptomatic hypoglycemia and a known family history of diabetes. Mildness of the underlying diabetes is indicated by the fact that the fasting blood sugar exceeded 110 mg. % in only 1 patient.

We believe that an early aberration of carbohydrate metabolism in diabetes mellitus consists of diminution in the speed of activation of increased glucose utilization. This results in postprandial hyperglycemia, sustained for 2 to 3 hours, followed by delayed but intense activation of insulinogenesis and hypoglycemia. This situation must not be confused with functional hyperinsulinism, in which postprandial hyperglycemia does not occur.

Early diabetes mellitus should be considered in patients presenting symptomatic spontaneous hypoglycemia. When this situation exists, proper management of the diabetes results in disappearance of the secondary hypoglycemia.

Observations on the Use of 10% Glucose in the Early Treatment of Diabetic Acidosis

By *Thomas B. Skilman, Margaret F. Kessler and Harvey C. Knowles, Jr.* Department of Medicine, University of Cincinnati College of Medicine, Cincinnati, Ohio.

Because few large clinical series concerning the effects of excess glucose in the treatment of diabetic

acidosis have been reported, studies to observe these effects have been made on 128 diabetic patients consecutively hospitalized with serum CO_2 contents of 14 mM/L. or less due to ketoacidosis. Fifty-one patients received 10% glucose solution i.v. during the first 6 hours of therapy regardless of initial blood sugar concentration or clinical condition. The remaining 77 control patients received no glucose or 5% glucose from onset. Other therapy was similar in both groups and followed conventional treatment schedules.

Statistic analysis of admission findings in the 2 groups revealed no differences between mean ages, levels of consciousness, precipitating factors, serum CO_2 contents, blood sugar and urea nitrogen concentrations or severity indices. Analysis of treatment schedules revealed no quantitative differences in administration of insulin, water or salt. The patients given 10% glucose received on the average 264 Gm. of glucose in the first 6 hours, while the control group received 104 Gm. ($p < 0.01$).

Observations during the first 6 hours of therapy revealed, for the 10% glucose and control groups respectively, mean urine volumes of 2.07 and 1.30 L. ($p < 0.01$), mean positive water balances of 1.10 and 1.93 ($p < 0.01$), mean changes in blood sugar concentrations of +16 and -179 mg. % ($p < 0.01$), and mean disappearance times of urinary ketones of 7.32 and 9.40 hr. ($p < 0.01$). The mortality rates of the 10% glucose and control groups were 29.4 and 35.9% ($p > 0.5$) respectively.

It is concluded that the administration of hypertonic glucose (10%) at the onset of therapy of diabetic acidosis results in continuation of hyperglycemia, sustained polyuria and diminished positive water balance. Although the period of ketonuria was shortened in the 10% glucose group, no significant difference of mortality was noted.

Correction of Metabolic Abnormalities in Diabetes Mellitus by Continuous Fructose Feeding

By *J. A. Moorhouse and R. M. Kark*. Department of Medicine, Presbyterian Hospital and the Department of Medicine, Research and Educational Hospitals, University of Illinois College of Medicine, Chicago.

Diabetics are able to utilize fructose, but this has not been of value in dietary management. Regardless of practical application, it was of interest to see whether diabetes could be controlled without insulin by the use of fructose under suitable conditions. It was thought that continuous 24 hr. feeding of a diet in which fructose was the only carbohydrate might restore liver glycogen, inhibit glycogenolysis and lower blood sugar. This was accomplished by the administration of a synthetic liquid diet by intragastric tube and feeding pump for periods of several days or weeks. Either glucose or fructose constituted the only carbohydrate, and

all other elements in the diet were left constant. Suitable blood and urine analyses were carried out.

In 3 of 4 patients with diabetes of moderate severity there was a well-defined fall in blood and urine levels of glucose and acetone during fructose feeding, together with diminished urinary excretion of potassium, phosphate and nitrogen. In 1 patient these effects were maintained during 3 weeks of fructose feeding and persisted after he was put back on a normal diet. One moderate diabetic and 2 severe diabetics showed little or no effect. An acromegalic patient with insulin resistant diabetes showed no change in glucose levels, but blood acetone fell markedly.

A Study of the Lactic Acid Production Occurring following Intravenous Fructose Infusions in Dogs

By *M. Richard Katz and C. Barber Mueller*. Washington University School of Medicine, St. Louis, Missouri.

The hemic concentration of lactate and pyruvate increases when fructose is administered intravenously to human beings and dogs. Such changes are not observed following the intravenous infusion of glucose. The biologic and chemical implications of these phenomena are unknown. These experiments were performed in an attempt to gain some insight into the mechanisms involved.

Fructose (10% in water) was given intravenously to dogs alone and before and after the administration of sodium lactate (3, 6 and 12 Gm.%). The rate of removal of lactate from the blood is proportional to its concentration in the blood, and lactate is eliminated more rapidly from the plasma at higher concentrations achieved following the infusion of lactate than at low concentrations resulting from the infusion of fructose.

The rate of removal of lactate from the blood is not altered by preloading the animal with an intravenous infusion of fructose just before the infusion of sodium lactate. The infusion of fructose after the infusion of sodium lactate raises the blood lactate concentration to the same extent that it does when given alone, and does not alter the slope of the disappearance curve.

The infusion of dihydroxyacetone (an intermediary product of hepatic fructose conversion) is followed by a rapid rise in blood lactate concentration. This suggests that the liver is the site of lactate production associated with the administration of fructose.

These experiments were designed to test the possibility that the rise in blood lactate following the infusion of fructose was related to the competition by fructose and lactate for the enzyme system in liver involved in the conversion of lactate to glucose. These experiments do not support this theory.

Application of Neutron Activation of Tissue to the Study of Muscle Electrolytes in Progressive Muscular Dystrophy and other Muscular Disorders

By *J. D. Williams, L. Reiffel, B. M. Ansell, C. A. Stone, J. Schoenberger and R. M. Kark*. Department of Medicine, Presbyterian Hospital, and Research and Educational Hospitals, University of Illinois College of Medicine, and the Armour Research Foundation of Illinois Institute of Technology, Chicago.

Serial study of tissue electrolyte concentrations is prohibited by the size of sample required for analysis by present technics. The use of neutron activation of small tissue samples was explored.

Neutron activation refers to the radioactivation of elements following bombardment with neutrons. The activated elements may be distinguished from each other by reason of their distinctive types of emission, energy values and decay rates. It was evident that the analysis of sodium, potassium and phosphorus would be particularly amenable to activation technics, even to millimicrogram levels.

The method was applied to the analysis of muscle samples of the order of a few mg. of fresh tissue and the results found to compare favorably with those from larger samples using other methods. Twenty-six samples from 23 patients were analysed for sodium, potassium and phosphorus content. Nine consisted of normal muscle, 10 were from cases of progressive muscular dystrophy and 7 from patients with a variety of muscular disorders. Further samples were examined histologically and for non-collagen nitrogen (NCN) content.

Potassium levels were significantly lower in the dystrophic group (mean 2.27 mEq./Gm. NCN) than in the normals (4.06 mEq.). Similarly significant was the higher sodium content of the dystrophic muscle (mean 3.43 mEq./Gm. NCN) compared with the normal (1.27 mEq.). The phosphorus levels did not differ significantly.

It is concluded that neutron activation provides a method suitable for electrolyte analysis of small tissue samples.

The Effect of Carbon Dioxide on the Concentration of Calcium in Ultrafiltrate of Serum Obtained by Centrifugation

By *Ananda S. Prasad and Edmund B. Flink*. Department of Internal Medicine of the University of Minnesota and the Medical Service of the Minneapolis Veterans Hospital, Minneapolis, Minnesota.

A simple, practical method has been devised for obtaining an ultrafiltrate of serum using a standard centrifuge. The serum is contained in a U

tube of Visking casing supported in a centrifuge tube by gauze. It is possible to obtain 3.0 ml. of ultrafiltrate from 10 ml. of serum in 75 min. by centrifuging at 2500 rpm. The serum was handled in four different ways: (1) The venous blood was collected and the serum separated anaerobically using a mineral oil seal. The Visking casing and the centrifuge tube were flushed with 5% CO₂ and 95% O₂ (O₂-CO₂ mixture). The serum was carefully transferred to the casing. (2) The same procedure was carried out as in (1) but at 37.5° C. In addition, the serum was handled from the time of separation from cells under oil to the sealing of the centrifuge tube in an atmosphere of the O₂-CO₂ mixture. (3) The serum was separated and placed in a flask and the O₂-CO₂ mixture was bubbled through the serum.

(4) The serum was separated and handled without any anaerobic precautions. pH was determined on the serum residue of (1) to (3) at the end of centrifugation.

The mean ultrafiltrable calcium expressed as % of the total calcium by the above methods was found to be 53.3 ± 2.48 for (1), 50.4 ± 3.75 for (2), 66.7 ± 4.79 for (3) and 52 ± 3.98 for (4). Prolonged bubbling of the O₂-CO₂ mixture caused a significant increase in the amount of ultrafiltrable calcium, although the ranges of pH values for groups (1) to (3) were the same.

Ultrafiltrable calcium obtained by the anaerobic handling of serum resulted in values of the same order of magnitude obtained for calcium ions by McLean and Hastings using their biologic method.

GASTROINTESTINAL SYSTEM

Studies on the Secretion of Pepsinogen, Acid and Water into Human Gastric Juice

By Basil I. Hirschowitz, John London and H. Marvin Pollard. Gastrointestinal Research Laboratories, Department of Internal Medicine, University Hospital, Ann Arbor, Michigan.

The question of whether histamine stimulates true secretion of gastric pepsinogen or merely washes out preformed pepsinogen from the canaliculi has been investigated by studying the relation between pepsin, volume and acid of the gastric contents under varying conditions. Estimations were made on $\frac{1}{4}$ -hourly samples of continuously aspirated gastric juice over periods of 4 to 14 hours in 20 normal human subjects under basal conditions, during vagal stimulation with intravenous ethyl alcohol or hypoglycemia, during long-continued intravenous histamine stimulation and during atropine, hexamethonium or Diamox depression of basal or stimulated secretion.

The selective depressant action of atropine on the water and pepsin, leaving the acid unaffected; and of Diamox on the acid, leaving water and pepsin unaffected; of histamine-stimulated gastric juice, and the depression by atropine of volume, acid and pepsin of vagally stimulated gastric juice indicate that pepsin and water are stimulated only by a cholinergic mechanism which is apparently capable of being activated by histamine. However, the stimulation of acid production through carbonic anhydrase may be effected either by acetylcholine, as it normally is, or directly by histamine acting without the intervention of acetylcholine.

The output of pepsin and of acid correlate in a linear fashion over the whole range of basal, depressed and stimulated secretion even in the most prolonged experiments. If preformed pepsinogen

were being washed out of the canaliculi by an increased flow of acid-water, the output of pepsin would be expected to lag behind that of acid after prolonged stimulation, but since this did not happen either with histamine or other stimulants, and because pepsinogen is secreted from different cells than the acid, it is indicated that these stimulants produce a true secretion of pepsinogen as well as acid.

The Effect of Intravenous Diamox on Gastric Secretion in Man

By E. Clinton Texter, Jr. and Hubbard W. Smith. Department of Medicine, Northwestern University Medical School and the V. A. Research Hospital, Chicago.

The secretion of gastric HCl can be inhibited in experimental animals following the intravenous administration of the carbonic anhydrase inhibitor acetazoleamide sodium (Diamox). Studies were carried out to determine the effect of intravenous administration of Diamox (10 mg./Kg.) on basal gastric secretion in man. After an hour control period, the sodium salt of Diamox was administered i.v. The rates of gastric secretion during the control and the 1-hour Diamox period were determined. CO₂ and blood pH measurements were made during the studies. Observations were made on 12 patients with duodenal ulcers. Six patients had control studies during the 1st hour followed by intravenous Diamox with the following results: control volume, 73 ml.; following Diamox, 61 ml.; control HCl, 83 mg.; following Diamox, 36.5 mg. Five out of the 6 subjects showed a definite fall in acid values.

In 6 additional ulcer patients, intravenous water was given at the beginning of the 2nd hour and intravenous Diamox at the beginning of the 3rd

hour with the following results: control volume, 92 ml.; following water, 69 ml.; following Diamox, 88 ml.; control HCl, 102.6 mg.; following water, 58.9 mg.; following Diamox, 32.2 mg. Five out of the 6 subjects showed an appreciable decrease in HCl recovery. These observations suggest that i.v. Diamox (10 mg./Kg.) depresses HCl production. This inhibition of secretion did not appear to be dependent upon alterations in acid-base balance of the blood, as reflected by blood pH and serum CO₂ determinations.

The Effect of Various Therapeutic Agents on the Gastric Hyperchlorhydria Induced by Intravenous Reserpine

By *Mervin L. Clark and Edward M. Schneider*.
Department of Medicine, University of Oklahoma School of Medicine and the V. A. Hospital, Oklahoma City.

The mode and site of action of Reserpine is as yet unknown. It is supposed that the effects of reserpine are either sympatholytic or parasympathomimetic and are centrally mediated (hypothalamus?).

In man and dogs intravenous reserpine produces a definite gastric hyperchlorhydria, as demonstrated by several observers. This response is not unexpected in view of the theoretic pharmacodynamics of this agent. In dogs this hyperchlorhydria can be blocked by an anticholinergic agent (oxyphenonium bromide). In order to determine whether or not this action of reserpine in man could be altered by various therapeutic agents, this study was undertaken.

A control group of 24 patients was studied, each patient being observed for a period of 240 min. after the administration of 1 mg. of Reserpine i.v. Hyperchlorhydria was noted to occur within 30 min. after the exhibition of the drug, and was sustained for the remainder of the period of observation. This was in marked contrast to the findings in 11 of the above subjects who received intravenous saline in a second study and developed no significant change in gastric acidity during 4 hours of observation.

Three groups of 10 patients were studied in a similar manner with Reserpine and simultaneously received 1 of the following drugs: (a) Atropine, 0.3 mg. i.v. No significant effect was observed over a 240 minute period. (b) Methantheline bromide (Banthine), 50 mg. i.v. A significant suppression of gastric acidity was observed at 30 min., but not thereafter. (c) Epinephrine (1:1000) 0.4 cc. subcutaneously. No significant alteration of Reserpine response was obtained during the 240 min. observation period.

These findings, although shedding no further light on the specific site or mode of action of Reserpine, serve to point out that atropine, methantheline bromide and epinephrine in therapeutic doses do not

effectively alter the undesirable parenteral Reserpine "side effects" of gastric hyperacidity in man.

The Effect of Oral Ethyl Alcohol on Hepatic Transaminase and Choline Esterase Activity and Pyruvate Concentration in the Rat

By *Keith S. Menley and M. Marvin Pollard*. Gastrointestinal Research Laboratories, Department of Internal Medicine, University Hospital, Ann Arbor, Michigan.

To determine whether alcohol acts directly on the liver, 3 groups of 7 rats received tap water, 10% alcohol and 20% alcohol respectively as the sole source of fluid, while on an unrestricted food intake for 16 days.

The animals were then killed, following which the ratio of liver to body weight was determined for each animal, and a specimen of liver from 1 member of each group examined histologically. The glutamic oxalacetic transaminase activity (GOT) and pyruvate concentration were determined in blood and liver homogenate, the acetyl choline esterase, and glutamic pyruvic transaminase (GPT) were determined in liver homogenate only.

Evidence for a direct action of alcohol on the liver was suggested by the following findings: compared with the control animals, and despite a gain in weight in all 3 groups, the alcohol-fed animals showed a decrease in the ratio of liver to body weight; their livers showed fatty changes and exhibited a very marked decrease of choline esterase concentration. Furthermore, the animals receiving 20% alcohol showed a significant increase of hepatic GPT activity, and a near-significant increase of hepatic GOT activity as compared with the controls, while the GOT activity of the blood was nearly equal in all 3 groups.

The incidental finding of a significantly raised blood pyruvate in the alcohol fed animals, which was reflected in similar changes in the hepatic pyruvate concentration, suggests possible pathways in the intermediary metabolism of alcohol other than those previously accepted.

The Effect of Carbon Dioxide, Exercise, Hyperventilation, Body Position and Degree of Pulmonary Inflation on Pulmonary Anatomic Dead Space

By *Russell H. Wilson and Bruce E. Jay*. University of Texas Southwestern Medical School, Dallas, and the V. A. Hospital, McKinney, Texas.

Evaluation of pulmonary function is not complete without an estimation of the anatomic and physiologic respiratory dead space. W. W. Stead showed the significance of an increase in dead space during thoracic surgery. Tracheotomy has also been used to decrease anatomic dead space in patients with respiratory acidosis. Krögh and Lindhard

concluded that dead space varied slightly during lung inflation; however, Haldane and Priestley found it to increase as much as 1200 ml. during severe exercise. W. S. Fowler, with the nitrogen meter and pneumotachograph, devised a method of measuring what was indicated as "physiologic dead space." This method of treating the volume-flow data of the nitrogen and pneumotachographic curves has been evaluated.

The purpose of this paper is to present a new method of analyzing the nitrogen meter curves for calculating anatomic pulmonary dead space. The method has been checked with the Bohr formula and found to yield identical values for respiratory anatomic dead space. A model was constructed with variable dead spaces to check the new method.

Our method of analysis of dead space nitrogen meter expiratory curves simplifies the problem, so that respiratory dead space can be readily calculated in patients with severe emphysema before and following thoracic surgery regardless of the respiratory pattern. Anatomic dead space has been measured with this method in 63 normal persons with an age range from 12 to 63 years, during exercise, rest, sitting, and supine positions, hyperventilation, and 8% carbon dioxide during a 20-min. period of breathing.

Comparative Evaluation of Bronchodilator Agents by Ventilatory Measurements: Epinephrine and Aminophylline

By Richard O. Sternlieb, Robert A. Pribek, Milton J. Fox and Ross C. Kory. Cardiopulmonary Laboratory and Medicine Service, Wood V. A. Hospital, and the Department of Medicine, Marquette University School of Medicine, Milwaukee, Wisconsin.

Although ventilatory function tests have been used extensively in the evaluation of newer broncho-

dilator agents, no such systematic studies have been carried out with epinephrine. In the present study, the bronchodilator effect of 0.3 mg. of subcutaneous epinephrine was compared with that of 0.5 Gm. of intravenous aminophylline by means of serial measurements of ventilatory function.

Twenty-four untreated male patients with definite bronchospasm were studied by means of total and timed vital capacity and maximum breathing capacity measurements before, and at 10, 30 and 60 min. after administration of each bronchodilator. Only one drug was administered on a single day, the other drug being tested at the same hour on a subsequent day. Epinephrine was given first in some patients, aminophylline in others.

The total vital capacity (VC) showed a greater increase after epinephrine in 15 patients and an increase equal to aminophylline in 6 patients. In only 3 patients was the VC increase greater with aminophylline. There was an average increase in VC of 17.8% after epinephrine as compared with 11.9% following aminophylline.

The maximum breathing capacity (MBC) showed a greater increase after epinephrine than aminophylline in 14 patients and an equal response in another 5. The average increase in MBC after epinephrine was 28.2%; after aminophylline, 15.5%.

The maximal midexpiratory flow (MMEF, Fowler), increased to a greater degree after epinephrine in 13 patients, with an equal response in 4 patients. The average increase in MMEF after epinephrine was 28%; after aminophylline, 21%.

The 1-sec. vital capacity increased an average of 16% after both drugs. The 3-sec. vital capacity increased only 3% following epinephrine; 2% after aminophylline.

It is concluded that subcutaneous epinephrine in 0.3 mg. dosage is somewhat more effective as a bronchodilator than 0.5 Gm. of intravenous aminophylline as measured by ventilatory tests.

INFECTIOUS DISEASES

The Demonstration of Cold Agglutinins due to *Listeria Monocytogenes* in Man and Rabbits

By R. J. Korn, V. J. Yakulis, C. E. Lemke and B. Chomet. Clinical Laboratory and Department of Medicine, West Side V. A. Hospital, Chicago, Illinois.

The demonstration of cold agglutinins in the serum of a patient with *Listeria monocytogenes* meningitis led to further agglutination and absorption studies of this patient and of rabbits in whom cold agglutinins were produced by the injection of killed *Listeria* organisms. *Listeria monocytogenes*

has been known to cause a purulent meningitis in man as well as in many animals. It has also been postulated as a possible etiologic agent in infectious mononucleosis, the organisms having been recovered from patients with the usual symptoms, physical and hematologic findings of that disease and with positive Paul-Bunnell tests. After our patient recovered from meningitis, he had a persistent lymphocytosis. Although heterophil antibodies were not found, cold agglutinins to sheep red cells were noted, and cold agglutinins to human red cells were also demonstrated. The latter observations may provide an explanation of the previously described

apparently positive heterophil antibody tests in cases of "infectious mononucleosis" caused by *Listeria monocytogenes*.

Recurrent episodes of illness in this patient were manifested by high titers of cold agglutinins and increased titers of *Listeria* agglutinins. The injection of killed *Listeria* organisms into rabbits produced significant titers of cold agglutinins as well as *Listeria* agglutinins. Absorption studies have also shown a relationship between this patient's cold agglutinins and *Listeria* agglutinins.

A Morphologic Comparison of the Organisms Found in Isolated Lung Nodules of Histoplasma Reactors with the Organisms Found in Acute Disseminated Histoplasmosis

By *Martin A. Segal*, V. A. Hospital,
Minneapolis, Minnesota.

Puckett was the first to describe histoplasma capsulatum organisms in the necrotic portions of pulmonary granulomas that had previously lacked demonstration of an etiologic agent. His work has provoked considerable controversy. There have been two principal criticisms: (1) that the microscopic morphology is not compatible with that of histoplasma capsulatum—the organisms are too large, their nuclei are too small, they do not stain with hematoxylin and eosin, they are extracellular; (2) that morphology alone without cultural proof is inadequate to identify the bodies seen as *H. capsulatum*.

A case has recently been studied at the Minneapolis V. A. Hospital which may serve to bridge the gap between the bodies described by Puckett and *H. capsulatum*. The organisms found in isolated lung nodules were compared with those found in this bacteriologically proven case of fatal disseminated histoplasmosis. Intracellular forms typical of *H. capsulatum* were found in the blood, bone marrow, liver, spleen and lungs by H & E stains. In addition to the disseminated lesions there was a necrotic focus in the right lung which afforded the opportunity for this study. In this necrotic material no organisms could be identified with H & E stain. With periodic acid-Schiff stain, however, forms were seen which were morphologically identical with those described in necrotic material by Puckett. All variations of these forms from the classic intracellular forms of histoplasma capsulatum to those described by Puckett could be identified in the sections from this one proven case. These can be demonstrated by color photomicrographs. It was concluded that the organisms described by Puckett are morphologically compatible with *Histoplasma capsulatum*.

The Association of Histoplasmosis and Lymphoma

By *Norman A. Nelson*, *Herbert L. Goodman* and *Harold L. Oster*, Department of Medicine, Wayne County General Hospital, Eloise, Michigan.

There are many reports in the literature which cite involvement of the reticuloendothelial system by more than one disease process. The frequency of tuberculosis and Hodgkin's disease in the same patient is well known. Concurrent histoplasmosis and tuberculosis is unusually common. It has been stated that 50% of lepromatous lepers die of tuberculosis. Zimmerman studied 74 cases of cryptococcosis and found that approximately $\frac{1}{3}$ represented *Cryptococcus* infection complicating pre-existing malignant lymphoma or leukemia. Other fungus diseases such as *Trichophyton rubrum* have been associated with malignant involvement of the reticulum.

It is the purpose of this report to consider the association of histoplasmosis and malignant lymphoma by presenting 2 additional cases and by means of a review of the literature.

The first patient had a chronic dermatitis for 11 years and was hospitalized several times for pneumonitis. Many peripheral blood examinations, 2 skin biopsies, 2 bone marrow studies and 1 lymph node examination were all compatible with chronic lymphocytic leukemia. The second patient also had many peripheral blood examinations, 2 bone marrow studies and 2 lymph node examinations, all of which were compatible with lymphoblastic lymphoma. Vigorous and persistent attempts to isolate *Histoplasma capsulatum* were fruitless. Both of the patients responded to therapy in a manner consistent with the diagnosis of lymphoma. At autopsy, disseminated histoplasmosis was found in both patients but the evidence for lymphoma was equivocal.

With this report, 17 cases will have been published. *Histoplasma capsulatum* was found histologically in all 16 autopsied cases. The malignant involvement of the reticulum was definitely substantiated in only 12 of the 16 at post-mortem examination even though the diagnosis was well established by ante-mortem biopsy.

Infection with disseminated histoplasmosis should be considered in every case of malignant lymphoma, especially if there are associated mucous membrane lesions.

An Evaluation of the Effectiveness of Cortisone Alone and in Combination with Oxytetracycline in Experimental Peritonitis in Rabbits

By *S. M. Farhat*, *D. M. Fitch*, *H. W. McFadden, Jr.*, and *M. M. Musselman*, Departments of Microbiology, Pathology and Surgery, University of Nebraska College of Medicine, Omaha. (Supported by a grant from Chas. Pfizer & Co., Inc.)

We have evaluated the effect of cortisone in the treatment of experimental peritonitis in rabbits as a guide to its use in patients with peritonitis. Cortisone has been reported to be of benefit in the treatment of patients with severe infections in general, and peritonitis in particular. However, ac-

cording to other evidence, cortisone may be deleterious in the management of infections.

We produced peritonitis in rabbits by devascularizing the appendix, ligating it at its base and incising it from base to tip. One group of untreated animals served as controls. A 2nd group was treated with oxytetracycline for 5 days after operation; a 3rd group with cortisone; and a 4th group with both oxytetracycline and cortisone in corresponding dosages. Animals living less than 24 hours were excluded from the study. Animals dying in the experimental period were examined, cultures taken from the peritoneal cavity and specimens of peritoneum, kidneys, liver, adrenals, lungs and heart were taken for biopsy. Animals surviving for 2 weeks were killed, and examined in a similar fashion.

Of the 10 animals receiving no treatment, 6

died within 11 days. Of 10 animals receiving oxytetracycline, all survived. Of 10 animals receiving cortisone, 5 died within 6 days. Of 10 animals receiving cortisone and oxytetracycline, 1 died on the 7th day. The animals receiving no treatment or cortisone alone showed more diffuse and more severe fibrinopurulent peritonitis, and more pneumonitis than did the animals receiving oxytetracycline alone or with cortisone. The adrenals were normal in all animals. The bacteriologic findings were not remarkable.

In conclusion, in rabbits with experimental peritonitis, treatment with cortisone alone gave no benefit and interfered with localization of the infection. Administration of cortisone did not detract from protection given by oxytetracycline, as measured by survival during the experimental period, but it did interfere with localization of the infection.

KIDNEY

Repair of Glomerular Lesions in Toxemia of Pregnancy

By Victor E. Pollak, Conrad L. Pirani, Robert M. Kark, Robert C. Muehrcke, Vincent C. Freda and John B. Nettles. Department of Medicine, Presbyterian Hospital, and the Departments of Medicine and Obstetrics, Research and Education Hospitals, and the Department of Pathology, University of Illinois College of Medicine, Chicago.

Since patients with toxemia of pregnancy rarely die, little is known about the pathology of the kidney in this disorder. A study was undertaken to correlate renal pathology with clinical and functional aspects of the syndrome. Fifteen women were studied during pregnancy at the height of the disease process, and 9 were restudied postpartum. Renal tissue was obtained by percutaneous needle biopsy.

All cases were characterized by hypertension during pregnancy. Most had edema and proteinuria, and the disease usually became manifest in the last trimester. In many, severe spasm of the retinal arterioles was striking.

Pathologically, the kidney of 1 patient was normal; 2 had benign nephrosclerosis; and in a 4th chronic glomerulonephritis with superimposed acute pyelonephritis were found. The other 11 patients had preeclampsia. Study of the renal biopsy specimens in this group disclosed thickening of the glomerular basement membrane. This thickening was diffuse, affected the entire glomerulus and every glomerulus in the sections. There was no hypercellularity. The thickening appeared to be due to swelling or edema of the basement membrane rather than to an increased deposition of mucopoly-

saccharide material, as demonstrated in Hotchkiss-McManus preparations. Proteinaceous material was often present in Bowman's spaces and in the lumina of the convoluted tubules. The tubular epithelium was somewhat flatter than normal and presented mild degenerative changes. Interstitial tissue and vessels were normal. All but 1 of the patients recovered after the delivery. In those who were studied again postpartum, the histologic appearance of the kidney had reverted to normal, and the glomerular basement membrane was thin and delicate.

However, in 1 patient definite thickening of the glomerular basement membrane was noted in addition to swelling. Hotchkiss-McManus preparations showed increased deposition of mucopolysaccharides. Hypertension persisted after delivery; the patient developed severe arteriolar sclerosis of the kidney, and thickening of the glomerular basement membrane persisted.

Correlations of Renal Structure and Function as Shown by Serial Renal Biopsy

By Victor E. Pollak, Robert M. Kark, Conrad L. Pirani and Robert C. Muehrcke. Department of Medicine, Presbyterian Hospital, Cook County Hospital, and the Research and Educational Hospitals, and the Department of Pathology, University of Illinois College of Medicine, Chicago.

The relationship between renal function and structural changes was investigated in a variety of diseases, using renal tissue obtained by percutaneous needle biopsy. Histologic sections were analysed semiquantitatively for changes in glomeruli, tu-

bules, interstitial tissue and vessels, and for over-all kidney damage.

The greater the thickening of the glomerular basement membrane, the greater was the proteinuria. However, proteinuria decreased as glomeruli became hyalinized and ischemic. There was no correlation between proteinuria and glomerular hypercellularity; but good correlations with the degree of tubular and over-all kidney damage were observed. Proteinaceous material was observed in Bowman's spaces and tubules of all cases with proteinuria, and in 11 out of 19 cases without proteinuria.

With few exceptions, blood creatinine and non-protein nitrogen levels were normal with lesser degrees of kidney damage, and exceeded 1.4 mg. % and 35 mg. % respectively only when kidney damage was severe. The degree of impairment of urea clearance reflected underlying renal damage. Maximum specific gravity correlated well with tubular and kidney damage; phenolsulfonphthalein excretion correlated better with tubular changes than with glomerular. In 7 of 10 cases good correlations were obtained between structural changes, inulin and PAH clearances, and TmPAH.

In some patients histologic kidney damage preceded biochemical and urinary abnormalities. By contrast, in hypokalemia severe derangement of kidney function was observed with minimal histologic changes. In nephrotic syndrome poor correlation with the underlying histologic picture was often found. Cases with membranous glomerulonephritis and others with predominant tubular damage showed similar functional derangements. Levels of serum cholesterol were highest in those with tubular damage and minimal glomerular changes.

The appearance of interstitial fibrosis coincided with a sudden increase in azotemia, the onset of hyperchloremic acidosis, and decrease in urea clearance. Compensation was re-established on a new level and further functional deterioration was gradual.

The Effect of Anemia and Polycythemia on Glomerular Filtration and Renal Vascular Tone

By *James F. Schieve*. Columbus, Ohio.

Anemia is associated with decreased, and polycythemia with increased renal blood flow. It is not clear whether these changes result from predominant efferent or afferent glomerular arteriolar vasomotor activity.

Forty-two patients without renal disease, whose hematocrits ranged from 17 to 80% and whose blood viscosity varied from 2.5 to 14 times that of water were studied. Renal clearances of para-aminohippurate (PAH) and mannitol were determined to obtain effective renal plasma flow (ERPF) and glomerular filtration rate (GFR) re-

spectively. Effective renal blood flow (ERBF) was estimated in the usual manner after Wintrobe hematocrit was corrected for PAH remaining in cellular layer. Hematocrit readings included the buffy coat. Blood viscosity was determined at 37°C. using an Ostwald pipet. Arterial blood pressure was obtained with a clinical sphygmomanometer. In all polycythemic patients, arterial blood oxygen saturation determinations were made. In an attempt to separate influence of hematocrit from that of viscosity, observations were also made in 7 patients with chronic myelogenous leukemia and twice in a patient whose total serum protein was 11.0 Gm. %.

An inverse linear relation was found between hematocrit and the GFR/ERBF ($r = -0.95$, 33 patients with hematocrits ranging from 17 to 73%). Similar results were found in secondary polycythemia ($r = -0.88$, in 9 observations with hematocrits varying from 54 to 80%). For a given hematocrit, however, the GFR/ERBF was consistently higher in the secondary group.

In 44 patients there was an expected linear relation between hematocrit and log of viscosity ($r = 0.98$). Leukemic and the elevated serum protein bloods showed inordinately high viscosity for their hematocrit. In these patients GFR/ERBF correlated better with hematocrit than with viscosity.

These observations suggest that in anemia and polycythemia the predominant factor in controlling renal blood flow may be the vasomotor activity of the efferent glomerular arteriole.

The Effect of Mercurial Diuretics on Kidney Succinic Dehydrogenase

By *Robert G. Page and Daniel Porte, Jr.* Department of Medicine, University of Chicago, Chicago. (Supported in part by the Douglas Smith Foundation of the University of Chicago.)

It has been demonstrated by histochemical techniques that mercurial diuretics in toxic doses inhibit succinic dehydrogenase in rat kidneys. In order better to quantitate this effect a different method was used. The amount of succinic dehydrogenase was measured for the whole kidney of rats. This determination was made possible by the fact that triphenyltetrazolium chloride (TTC) in the presence of substrate and dehydrogenase is reduced to a formazan, the color of which is red, and the concentration of which can be measured spectrophotometrically.

Young female rats of the Holzman strain were used either as controls or were injected with Dicurin. The dose employed was either 5 or 40 mg. Hg/Kg. of body weight. The animals were killed at appropriate times and the kidneys were removed and weighed. The kidneys were homogenized in saline, and aliquots were taken to determine dry weight as well as endogenous and exogenous re-

ducing activity. Endogenous activity was measured by the addition of TTC, distilled water and phosphate buffer, whereas sodium succinate was substituted for the distilled water to determine the exogenous plus the endogenous activity. After a 2-hour incubation, the reaction was stopped by the addition of trichloroacetic acid, and the color extracted with ethyl acetate. The results are expressed in units which represent the exogenous reducing activity in γ TTC/100 mg. of kidney dry weight.

These experiments confirmed the results of the experiments in which histochemical techniques were employed, showing that there is a significant inhibition of dehydrogenase when toxic levels of mercury are attained. No such inhibition occurred when therapeutic doses were used. The controls showed an average of 83.4 U (s.d. = ± 26.0 U). The 5 mg. Hg/Kg. animals averaged 86.0 U (s.d. = ± 16.8 U) and the 40 mg. Hg/Kg. animals averaged 43.2 U (s.d. = ± 23.5 U). Between the controls and the latter group the difference is highly significant, while it is insignificant between the controls and the former group.

From these studies it would appear that the therapeutic action of mercurial diuretics may well be related to some other mechanism than the depression of succinic dehydrogenase.

Some New Immunologic Studies on Purified Human Glomerular Basement Membrane and Dog Glomerular Basement Membrane In Vitro.

By *Raymond W. Steblay and Mark H. Lepper.*
University of Illinois School of Medicine, Chicago.

Dog glomerular basement membrane was prepared after the method of Krakower and Greenspon.

Human glomeruli were isolated in a similar fashion, and some of their physical properties studied. The practically pure (99%) yield of human glomeruli was vibrated in a sonic vibrator, disrupting the glomeruli into basement membrane fragments and cellular debris. By a process of centrifugation, decantation and washings, a relatively cell-free sediment of human basement membrane fragments was obtained.

The purified preparations of human and dog basement membrane were resuspended in saline to known concentrations, revibrated and used to immunize rabbits, with various adjuvants, concentrations, portals and injection frequencies. The rabbit antisera were obtained at frequent intervals.

It was demonstrated that: (1) human and dog basement membranes (revibrated to fine suspensions before testing) fixed complement with their respective antisera in vitro; (2) human basement membrane cross-reacted to a lesser but definite degree with antidog basement membrane sera in the complement fixation test. Likewise, dog basement membrane cross-reacted to a lesser but definite degree with antihuman basement membrane sera using the complement fixation test. In vivo studies on the nephrotoxic ability of the antihuman basement membrane sera have been carried out.

It is concluded that human glomerular basement membrane preparations of this degree of purity contain an antigen (or antigens) that can fix complement against its own antiserum in vitro; and this human antigen is identical with, or immunologically similar to, the complement-fixing antigen in dog basement membrane preparations of equivalent purity.

THERAPEUTICS

Therapeutic and Toxic Effects of Enteric-Coated Aminometramide

By *Walter A. Tatge, Donald E. Winnik and George N. Spencer.* Medical Service, Wood V. A. Hospital, and the Department of Medicine, Marquette University School of Medicine, Milwaukee, Wisconsin.

Aminometramide (Mictine), a 6-aminouracil, has been found to possess safe and fairly effective diuretic activity, although the mode of action is not known. Thus far, the principal objection to this promising oral diuretic in uncoated form has been a high incidence of annoying gastrointestinal symptoms at therapeutic levels. The purpose of this study was to evaluate an enteric-coated preparation.

This drug was administered to 9 edematous

patients with portal cirrhosis, 2 patients with nephrosis, and 18 members of an out-patient cardiac clinic. Six of the cirrhotics exhibited significant diuresis. One patient with nephrosis experienced dramatic diuresis, which was felt to be spontaneous rather than induced. Fourteen of the 18 cardiac patients lost edema or maintained dry weight during the study.

Frequent side effects were encountered, since this was in part an evaluation of tolerance. These consisted of anorexia, constipation, nausea or vomiting. They were uniformly minor in degree, and usually followed exorbitant doses after prolonged, continuous administration. No untoward effects were observed in patients with chronic hepatic, renal or cardiac disease. There was no evidence of electrolyte disturbances. A perceptible margin appeared to exist between therapeutic and

toxic levels. Therapeutic dosage was in the range of 800 mg. daily, in divided doses. An intermittent schedule was not carried out in this study.

It is concluded that with an individualized therapeutic program, enteric-coated aminometramide promises to be a safe, effective and fairly well-tolerated oral diuretic.

An Evaluation of the Usefulness of Chlorpromazine in Patients on a Surgical Service

By *Harold D. Jourdan and M. M. Musselman.*
Department of Surgery, University of Nebraska
College of Medicine, Omaha.

In the past 4 years investigators have studied the properties of Chlorpromazine and its clinical applications. The observed pharmacologic effects of Chlorpromazine suggested that it might alleviate nausea, vomiting and pain in surgical patients. We

have administered Chlorpromazine to 105 patients with nausea, vomiting or pain refractory to narcotics, to determine its effectiveness in relieving these symptoms. Also, we compared the effectiveness of a 10 mg. dose with that of a 25 mg. dose, and the effectiveness of oral with that of intramuscular administration.

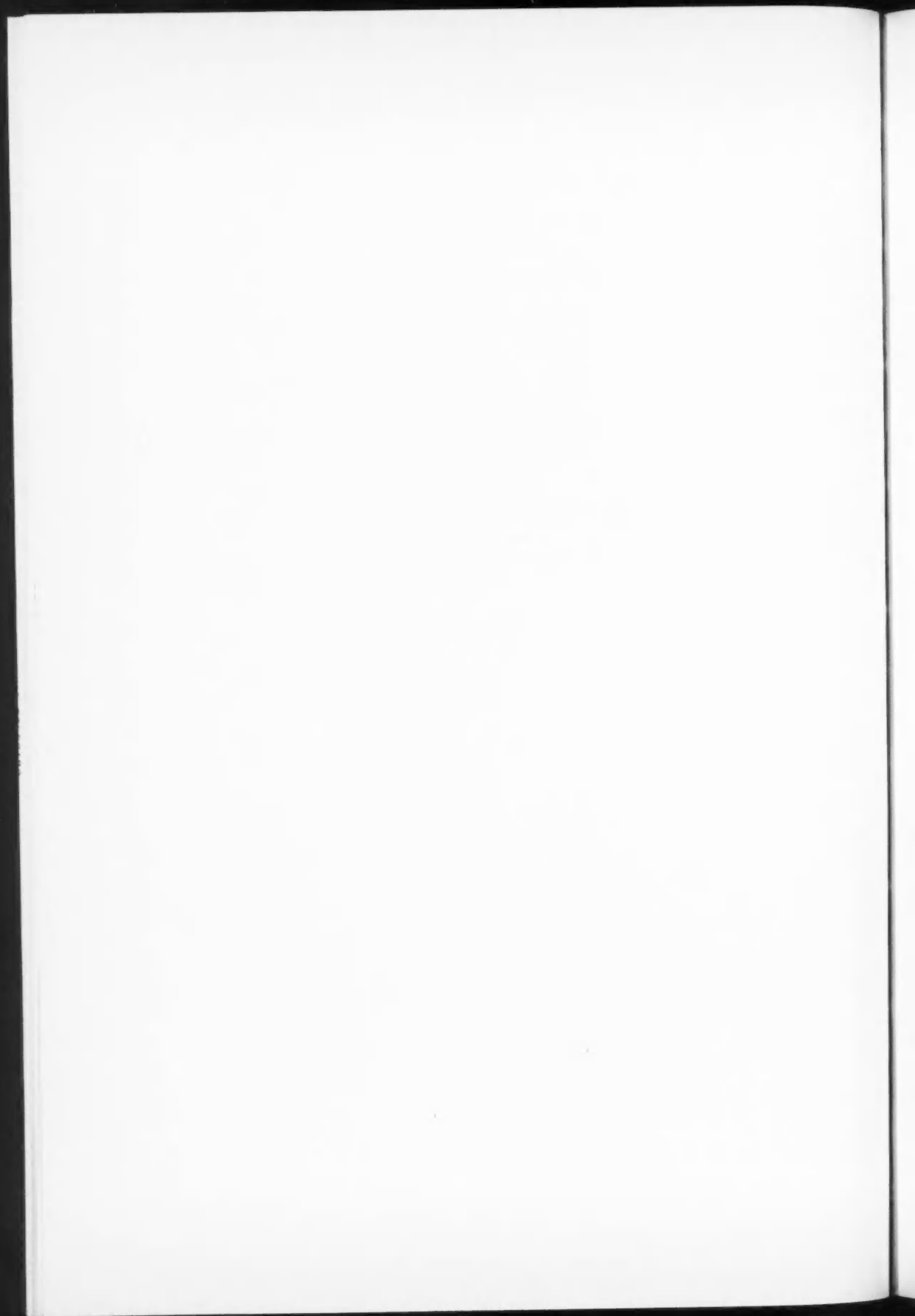
Chlorpromazine intramuscularly was effective in relieving symptoms in patients after operation. Relief was obtained with a dose of 10 mg., but 25 mg. gave more prompt and more prolonged relief. Intramuscular administration gave prompter but no greater relief than oral administration.

Drowsiness was the only side effect of the administration of Chlorpromazine, and no toxic effects were noted. The use of Chlorpromazine intramuscularly did not mask symptoms or complicate the clinical course in diseases such as intestinal obstruction.

Clinical Research Proceedings

Volume III, 1955

INDEXES



Clinical Research Proceedings, Vol. III, 1955

No. 1, FEBRUARY

Current Comment: Why Not Control Hypertension with Drugs? *page 1*
 Abstracts Submitted to Sectional Meetings of the American Federation for Clinical Research:
 Midwestern Section, Chicago, October 1954, *page 6*
 Eastern Section, Washington D. C., December 1954, *page 27*
 Western Section, Carmel, Calif., January 1955, *page 51*
 Southern Section, New Orleans, January 1955, *page 67*
 Author Index (pp. 1-84), *page 83*

No. 2, APRIL

Current Comment: Reason and Imagination in the Understanding of Chronic Peptic Diseases, *page 85*
 Program, *page 89*
 Abstracts submitted to the National Meeting of the American Federation for Clinical Research, Atlantic City, May 1955, *page 91*
 Author Index (pp. 85-150), *page 149*

No. 3, SEPTEMBER

A Welcome Place, *page 151*
 Lilliput Revisited, *page 153*
 Host Factors and the Decline of Infection, *page 154*
 Notices, *page 157*
 Membership Roster: American Federation for Clinical Research, *page 159*

No. 4, NOVEMBER

Statistics, Sophistication, Sophistry and Sacred Cows, *page 185*
 The New Look in Medical Genetics, *page 187*
 Notices, *page 191*
 Program, *page 192*
 Advance Research Reports Submitted to the Annual Meeting of the Midwestern Section, Chicago, November 1955, *page 194*
 Annual Author Index, *page 215*
 Annual Subject Index, *page 219*

AUTHOR INDEX

- | | | | |
|----------------------------|--------------------------|----------------------------|----------------------------|
| Abbott, L. D., Jr., 93 | Baker, O., 134 | Blair, E., 66, 81, 147 | Burstein, S., 43 |
| Abbott, W. E., 18 | Balchum, O., 24, 115 | Blake, T. M., 73 | Butler, J. J., 99 |
| Abelmann, W. H., 54, 65 | Balfour, D. C., Jr., 62 | Blocker, T. G., Jr., 127 | Bynum, T., 21 |
| Adamis, D., 103 | Ballabio, C. B., 148 | Blount, S. G., Jr., 24, | |
| Adamkiewicz, L., 124 | Balke, B., 82 | 53, 107, 115 | |
| Adams, J., 56 | Barborka, C. J., 22 | Bolt, R. J., 22 | Caliva, F. S., 104, 108 |
| Adelson, B. H., 10 | Bashour, F., 198 | Bond, W. H., 195 | Caraway, L. D., 20, 141 |
| Adelson, E., 103 | Bauer, F. L., 32 | Boren, H. G., 25 | Carbone, J. V., 141 |
| Adler, S., 105 | Becker, G. H., 17 | Born, J. L., 130 | Case, R. B., 35, 96 |
| Adlersberg, D., 139 | Becker, R., 10 | Borun, E. R., 60 | Castle, W. B., 95 |
| Aikawa, J. K., 12, 55, 135 | Beechmans, M. L., 61 | Bossak, E. T., 139 | Cathcart, R. T., 146 |
| Albert, D. G., 116 | Beer, B. V. A. L., 130 | Bossi, E. E., 146 | Caylor, H. D., 18 |
| Allen, A., 37 | Behrer, M. R., 199 | Bowers, J. Z., 148 | Chalmers, T. C., 141, 142 |
| Allenstein, B. J., 109 | Beierwaltes, W. H., 11, | Bradbury, J. T., 202 | Chaplin, H., Jr., 29 |
| Amira, A., 148 | 88, 151 | Brandfonbrener, M., 105 | Chapman, C. B., 191 |
| Amram, S., 35 | Beman, F. M., 131 | Braude, A. I., 77, 78, 134 | Charms, B. L., 198 |
| Andr n, H. E., 41 | Benjamin, N. R., 100 | Braunwald, E., 35, 108 | Chernick, S. S., 19 |
| Anger, H. O., 130 | Bennett, I. L., Jr., 154 | Braveman, W. S., 136 | Cheung, M. W., 97 |
| Ansell, B. M., 144, 204 | Benson, J. W., 18 | Brecher, G., 30 | Chinsky, M., 200 |
| Apt, L., 28, 92, 93 | Berman, H. J., 145 | Brick, I. B., 141 | Chodos, R. B., 91, 120, |
| Aravanis, C., 196 | Berman, L. B., 47, 148 | Brofman, B. L., 198 | 127 |
| Assali, N. S., 63 | Bernstein, L., 144 | Bronsky, D., 135 | Chofnas, I. C., 25 |
| Atuk, N., 67 | Best, W. R., 6, 99, 101 | Brow, R. E., 61 | Chomet, B., 207 |
| Auchincloss, J. H., Jr., | Bethell, F. H., 194 | Brown, D. N., 21 | Chu, L. S., 47 |
| 31, 147 | Beutler, E., 52 | Brown, H., 137 | Citrin, Y., 108 |
| Ausman, D. C., 199 | Bierman, H. R., 65, 99 | Brown, R. R., 201 | Clark, E. R., 133 |
| Ausman, R. R., 199 | Birchard, W. H., 142 | Browne, D. C., 79 | Clark, M. L., 78, 132, 206 |
| Ayres, S. M., 107 | Birenbaum, A., 39 | Bryant, J. M., 12, 196 | Clatanoff, D. V., 195 |
| | Bisel, H. F., 128 | Burch, G. E., 75 | Claudatus, J. C., 13 |
| Baker, C., 77, 78 | Bishop, R. C., 194 | Burchenal, J. H., 21 | Coblentz, A., 65 |
| Baker, L., 139 | Blahd, W. H., 64 | Burrows, B. A., 121 | Cochrane, G., 60 |
| | | | Cohen, L. D., 72 |

- Cohen, L. M., 15
 Cohen, R. V., 46
 Colbert, M. J., 28
 Cole, L. R., 27
 Collins, K., 132
 Colmore, J. P., 21
 Colville, V. F., 29, 46
 Conklin, E. J., 105
 Conn, H. L., Jr., 37, 111
 Conn, J. W., 122, 201, 203
 Cook, E., 31
 Corbus, H., 15
 Corrado, M. A., 47
 Costley, C., 202
 Cotton, M. deV., 70
 Courand, A., 114
 Cowley, R. A., 32, 111
 Coyne, R., 123
 Craig, J., 202
 Craighead, C. C., 79
 Crispell, K. R., 74
 Crosby, W. H., 100
 Crosley, A. P., Jr., 18
 Crumpton, C. W., 11
 Crutcher, J. C., 80
 Culbertson, J. W., 20, 141
 Curreri, A. R., 201

 Daeschner, W. C., Jr., 71
 Dalberg, L., 60
 Daley, R., 110
 Danzig, L. E., 106
 Darnell, J. E., 132
 Daughaday, W. H., 121
 Daughaday, W. H., 16
 Davis, J. H., 18
 Davis, J. O., 114
 Dawson, W. H., 34
 Dayman, H. G., 24
 DeFazio, V., 120
 DeFilippa, V., 201
 DeGroot, L. J., 42
 DeLor, C. J., 131
 Dempsey, M., 24
 Dennis, C., 105
 Dennis, E. W., 71
 Desai, R. G., 145
 Dexter, L., 110, 145
 Dobson, E. L., 55
 Dodge, H. T., 82
 Doering, C. R., 132
 Donoso, E., 108
 Donovan, T. J., 35
 Doolan, P. D., 64, 138
 Dorfman, R. I., 43
 Dorris, E. R., 133
 Downs, J. J., 132
 Dreskin, O. H., 32, 103
 Drucker, W. R., 202
 Dubin, A., 129, 135
 Duff, I. F., 196
 Duffy, B. J., 36, 126
 Dunning, M. F., 144
 Durant, T. M., 107

 Ebaugh, F. G., Jr., 91, 110
 Eckstein, J. W., 20, 141
 Eddleman, E. E., Jr., 70
 Edelman, I. S., 62
 Eich, R., 108, 147
 Eikenberry, D., 54
 Eisenberg, S., 25, 143
 Elgee, N. J., 122

 Eliel, L. P., 79, 80, 101
 Ellenbogen, L., 28
 Elster, S. K., 112
 Emerson, C. P., 92
 Emmett, R., 79
 Engle, R. L., Jr., 102
 Englert, E., Jr., 137
 Epstein, F. H., 45, 47, 48, 137, 138
 Eriksen, N., 104
 Erslev, A. J., 94
 Estes, E. H., 82, 136
 Evans, J., 197
 Evans, R., 24

 Fajans, S. S., 122, 203
 Faloan, W. W., 132
 Fancher, P. S., 32
 Farhat, S. M., 208
 Favour, C. B., 27, 133
 Fazekas, J. F., 115, 116
 Felts, P. W., 73
 Feys, J., 148
 Field, J. B., 61
 Fields, M., 64
 Finch, C. A., 52, 94
 Finch, S. C., 97
 Finkenstaedt, J. T., 137
 Fishman, A. P., 114
 Fitch, D. M., 208
 Flink, E. B., 204
 Ford, R. V., 14
 Fordham, C. C., III, 68
 Foreman, N., 60, 61
 Foster, J. J., 141
 Fowler, B. O., 109
 Fox, H. M., 73
 Fox, M. J., 207
 Frawley, T. F., 41
 Freda, V. C., 209
 Frederick, W., 70
 Freedman, M. S., 123
 Freinkel, N., 42
 Freireich, E. J., 92
 Freis, E. D., 35, 125
 French, A. B., 148
 Friedman, E., 140
 Fritss, H. W., 114
 Frumin, A. M., 29, 96
 Fulton, G. P., 145
 Furman, R. H., 75
 Furth, F. W., 95

 Gamble, J. R., 196
 Gardner, F. H., 8
 Geiger, E., 60
 Gelvin, E. P., 40
 Genest, J., 124
 Gensini, G., 24, 115
 George, D. J., 25
 Gerundo, M., 59
 Giblett, E. R., 52, 94
 Gibson, J. F., 71
 Gilbert, R., 147
 Gilbert, R. P., 10
 Gifillan, R. S., 55
 Gitlow, S. E., 91
 Glaser, R. J., 132
 Glauser, S. E., 8
 Glicksman, A. S., 142
 Goldman, A., 65
 Goldman, R., 64, 138
 Goldner, M., 124
 Goldring, D., 199
 Goldsmith, J. R., 146

 Gomez-Uscategui, J., 101
 Goodman, E., 146
 Goodman, H. L., 208
 Goodwin, R. A., Jr., 133
 Gorayeb, E., 105
 Gordon, A. J., 35
 Gordon, G. S., 56
 Gordon, M. E., 37
 Gorlin, R., 110, 115
 Grace, J. T., 113
 Grant, J. L., 146
 Gravalles, M. A., Jr., 38, 54
 Gray, S., 73, 131
 Greenberg, M. S., 95, 96
 Greer, M. A., 42
 Grekin, T. D., 50
 Griffin, J., 148
 Griffin, J. A., 10
 Griffin, R. A., 149
 Griffith, D. R., 196
 Griffith, H. W., 126
 Griffith, J., 146
 Griffith, W., 36
 Grishman, A., 108
 Gross, G., 202
 Gross, J. F., 113
 Grossman, C. M., 61
 Grossman, M. I., 17, 196
 Gubner, R., 39
 Guyton, A. C., 69

 Hagen, P. S., 9
 Halde, C., 66
 Handley, C. A., 25
 Haring, O. M., 12
 Harper, H. A., 64, 138
 Hartmann, R. C., 68
 Haynes, F. W., 110, 145
 Heaney, R. P., 79, 80, 101
 Heidorn, G. H., 17
 Heinemann, H. O., 97
 Hellems, H. K., 120
 Heller, B. G., 13
 Helm, R., 197
 Henck, E. A., 28
 Hendrix, T. R., 130
 Henegar, G. C., 61
 Henley, E. D., 122
 Hershenson, L. M., 110, 125
 Heyman, A., 80
 Hickam, J. B., 66, 71, 81
 Hicks, C. E., 107
 Hill, S. R., Jr., 73
 Hills, A. G., 124
 Himmelstein, A., 35
 Hinz, C. F., Jr., 6, 7
 Hinz, J. E., 9
 Hirsch, J., 108
 Hirschowitz, B. I., 22, 131, 205
 Hodgson, P. E., 196
 Hoefler, G., 79
 Hoffman, I., 38
 Holden, W., 202
 Hollander, W., 33, 49, 117
 Hollander, W., Jr., 68
 Holley, H. L., 72, 118
 Hollifield, G., 74
 Holmes, T. H., 133
 Honig, K. P., 10, 129
 Horn, P. W., 117
 Horsley, A. W., 20, 141

 Houghton, B. H., 94
 Howard, R. P., 75
 Howell, D. S., 114
 Howell, J. T., 7
 Hufnagel, C. A., 35, 109
 Huggins, C. B., 130
 Hughes, W. M., 71
 Huguley, C. M., Jr., 82
 Hultgren, H., 54
 Hurley, T. H., 7
 Huston, J. H., 11
 Huston, J. R., 197
 Hutchin, M. E., 64, 138
 Huth, E. J., 127
 Hyatt, R. E., 114
 Hydgem, R. D., 22

 Iber, F. L., 142
 Ingbar, B. H., 42
 Ingelfinger, F. J., 130
 Inkley, S. R., 11
 Iseri, L. T., 17, 116
 Izlar, H. L., 136

 Jacobson, S. D., 105
 Jager, B. V., 144
 James, G. W., III, 31, 93
 Jandl, J. H., 95
 Jankelson, O. M., 130
 Jay, B. E., 206
 Jefferies, W. McK., 14, 16
 Jenkins, C. D., 22
 Jensen, W. N., 67, 93
 Joel, W., 78
 Johns, T. N., 69
 Johnson, J. B., 113
 Johnson, P. C., 119
 Johnson, R. L., Jr., 81, 145
 Johnston, F. D., 12
 Jones, H. S., 46
 Jones, R. J., 15, 125
 Joseph, H. L., 66
 Jourdan, H. D., 212
 Judson, W. E., 33

 Kabakow, B., 28, 30
 Kaminski, J., 26
 Kaplan, B., 139
 Kaplow, L., 98
 Kark, R. M., 13, 115, 139, 141, 198, 203, 204, 209
 Karlson, K., 105
 Kass, E. H., 96
 Katz, M. R., 204
 Kaufman, B. N., 69
 Keating, R. P., 102
 Keitel, H. G., 29, 46
 Kelly, E., 34, 106
 Kelly, J., 81, 147
 Kelly, J. J., Jr., 107
 Kelly, K. H., 65, 99
 Kelly, L. W., Jr., 14, 16
 Kelser, G. A., 136
 Kemp, R. L., 123
 Kennedy, B. J., 200
 Kenyon, K. E., 63
 Kessler, M. F., 203
 Kimball, D. M., 103
 Kinsell, L. W., 60, 61
 Kipnis, D. M., 72
 Kistin, A. D., 39
 Kleeman, C. R., 45, 47, 48, 137, 138
 Kleh, J., 115, 116

- Kline, D. L., 97
 Knoll, H. C., 131
 Knowles, H. C., Jr., 203
 Knowles, J. H., 115
 Knowles, J. L., 70
 Knowlton, M., 141
 Koiw, E., 124
 Koler, R. D., 93
 Koprowska, I., 102
 Korn, R. J., 19, 207
 Korse, D. R., 20
 Korst, D. R., 195
 Kory, R. C., 133, 207
 Kotte, J. H., 197
 Kovach, R. D., 110, 125
 Kowalski, H. J., 54, 65
 Krakauer, L. J., 131
 Kramer, P., 130
 Kratochvil, C. H., 20
 Krieger, H., 18
 Kroop, I. G., 119
 Kuida, H., 110
 Kunkle, E. C., 72
 Kurnick, N. B., 56, 143
 Kushner, D., 129, 135
 Kyle, L. H., 36, 43, 47, 76, 141
 LaDue, J. S., 20, 37, 48, 49, 112, 119
 Lamdin, E., 45, 48, 138
 Landowne, M., 105
 Lange, K., 140
 Lange, R. D., 9
 Langford, H. G., 43, 73
 Lasagna, L., 185
 Lasser, R. P., 35
 Lathem, W., 37
 Lawrence, J. H., 130
 Leach, R. B., 73
 Lear, A. A., 95
 Leavell, B. S., 67
 Lee, S. L., 98, 101
 Leight, L., 120
 Lemire, R. E., 23
 Lemke, C. E., 207
 Lemon, H. M., 123
 Lepper, M. H., 211
 Levey, S., 18
 Levin, M. E., 16, 121
 Levin, W. C., 127
 LeVine, D., 56
 Levine, E. H., 138
 Levine, H. D., 109
 Levinger, E. L., 112
 Levowitz, B., 105
 Levy, H., 112
 Levy, R. P., 14, 16
 Lewis, S. R., 127
 Lichtman, H. C., 28, 30
 Liebhold-Schueck, R., 57
 Lilienfeld, L. S., 110, 125
 Lillehei, J. P., 82
 Lindsey, A. W., 69
 Lipsett, M. S., 138
 Lipsky, S. R., 45
 Litter, J., 117
 Loeb, V., Jr., 94
 London, J., 205
 Loyke, H. F., 143
 Lubin, R. I., 13
 Luchsinger, E. B., 138
 Luisada, A. A., 12, 196
 Lukas, D. S., 107, 147
 Luttgens, W. F., 51
 Lutz, B. R., 145
 Lynch, P. R., 107
 Lyons, H. A., 30, 107
 Lyons, R. H., 104, 108, 113
 McCord, M. C., 53, 107
 McCoy, E. E., 199
 McCreery, P., 56
 McCurdy, P., 91
 McFadden, H. W., Jr., 208
 McGavack, T. H., 40
 McGrath, T., 26
 McGuire, J. S., 45
 McIntosh, H. D., 82
 McIver, F. A., 201
 McKusick, V. A., 187
 McMaster, J., 29
 McMillan, I. K., 110
 McNeely, W. F., 38, 54
 MacDonald, F. M., 24
 MacDonald, R., 126
 Mackay, I. R., 104
 Maddock, W. O., 73
 Mader, I. J., 17
 Madison, L. L., 25, 76, 126, 136
 Magill, G. B., 21
 Magill, J. W., 21
 Manchester, B., 34
 Manniz, E. P., 109
 Marcus, P., 123
 Marks, P. A., 110, 125
 Martin, F. E., 24
 Martinez, E., 56
 Mason, J. D., Jr., 67
 Mason, S. R., 104
 Masouredis, S. P., 61
 Massullo, E. A., 35, 109
 Masuda, M., 133
 Mathews, K. P., 13
 Mattingly, T. W., 32, 36
 Mauck, H. P., Jr., 43
 Meacham, G. C., 97
 Mead, A. W., 136
 Medwid, A., 37
 Meinert, J. K., 11
 Mellins, R. B., 22
 Mendeloff, A. I., 85
 Meneely, G. R., 113
 Meng, H. C., 68
 Menley, K. S., 206
 Merrill, J. M., 113
 Merrill, J. P., 140
 Meyer, F. L., 201
 Meyer, R. J., 43, 76, 141
 Michaels, G. D., 60, 61
 Migeon, C. J., 148
 Milch, R. A., 129
 Miller, A., 92
 Miller, M., 202
 Miller, W. F., 81, 145
 Mitchell, M. L., 121
 Mitchell, R. A., 23
 Moeller, H. C., 196
 Moir, T. W., 11
 Moloney, W. C., 30, 98
 Moltan, L., 29, 46
 Monk, A., 63
 Monto, R. W., 7
 Moore, J. G., 62
 Moorhouse, J. A., 115, 198, 203
 Morgan, M. C., 102
 Morita, Y., 116
 Morrison, R. S., 140
 Moscovitz, H. L., 35
 Moser, M., 36
 Motulsky, A. G., 51, 94, 104
 Moyer, J. H., 71
 Muehrcke, R. C., 13, 139, 209
 Mueller, C. B., 204
 Mueller, J. F., 196
 Murawski, B., 73
 Murdaugh, H. V., 75
 Musselman, M. M., 208, 212
 Nadel, E. M., 43
 Nadell, J., 62
 Narahara, H. T., 58
 Nelson, N. A., 208
 Nettles, J. B., 209
 Newman, M. M., 105
 Newton, W. A., Jr., 195
 Nichols, G., Jr., 44, 125
 Nichols, N., 44, 125
 Noble, W., 109
 Nowaczynski, W., 124
 Nydick, I., 37, 112, 119
 Olson, B. J., 69
 Onesti, S. J., Jr., 53
 Oppenheimer, M. J., 107
 Orcutt, J. A., 55
 Oser, B. M., 197
 Osgood, E. E., 93
 Osman, K., 62
 Oster, H. L., 105, 208
 Ostfeld, A. M., 128
 Ostrow, B. H., 112
 Page, E. B., 67, 93
 Page, R. G., 210
 Pansky, B., 127
 Pappas, R., 70
 Parida, R. K., 141
 Parrish, A. E., 115, 116, 138
 Parson, W., 74
 Parsons, D. W., 124
 Paulsen, C. A., 73
 Payne, R., 51
 Penna, D., 107
 Penneys, R., 33, 40, 111, 118, 200
 Perkoff, G. T., 59
 Perry, J., 127
 Pesch, B. B., 132
 Peters, J. H., 80
 Peters, T., Jr., 93
 Peterson, R. E., 91
 Peterson, W., 51
 Petrakis, N. L., 55
 Peyton, W. T., 200
 Pfeiffer, J. B., Jr., 80
 Phear, E. A., 48
 Phil, D., 201
 Pierce, J. M., Jr., 137
 Pigman, W., 72, 118
 Piliero, S. J., 127
 Pincus, S., 70
 Pirani, C. L., 13, 139, 209
 Pisciotta, A. V., 9
 Platt, D., 72, 118
 Plough, I. C., 43, 142
 Plum, F., 144
 Pogge, R. C., 40
 Polhemus, J. A., 196
 Pollak, V. E., 139, 209
 Pollard, H. M., 22, 131, 205, 206
 Polycove, M., 28, 92
 Pomeranze, J., 127
 Pont, M. E., 201
 Pool, J. G., 52
 Poppell, J. W., 104
 Popper, H., 129
 Porte, D., Jr., 210
 Prasad, A. S., 194, 204
 Pribek, R. A., 207
 Price, J. M., 201
 Prior, J. T., 132
 Pritchard, J. A., 6
 Pritchard, W. H., 11
 Proctor, R. C., 149
 Prout, T. E., 142
 Rabiner, S. F., 28
 Rabinowitz, M., 145
 Rall, T. W., 17
 Ramsey, C. G., 131
 Randall, H. T., 104, 126, 142
 Rantz, L. A., 63
 Rapaport, E., 110
 Rath, C., 91
 Ravitch, M. M., 35
 Ray, C. T., 75
 Rayson, G. E., 26
 Rebusk, J. W., 7
 Redisch, W., 40
 Regan, T. J., 120
 Reid, A. F., 126
 Reiffel, L., 204
 Reisner, E. H., Jr., 28, 102
 Relman, A. S., 44
 Remenchik, A. P., 115, 198
 Renzetti, A., 31
 Reppert, E., 36
 Respass, J. C., 130
 Reynolds, M. L., 34
 Richmond, L., 196
 Rigas, D. A., 93
 Ritts, R. E., Jr., 27, 133
 Robb, G. P., 32
 Roberts, J. E., 130
 Roberts, K. E., 104, 126, 142
 Robertson, J. S., 37
 Robillard, R., 124
 Rodnan, G. P., 19, 91, 110, 125
 Rohn, R. J., 195
 Rohrsen, D. J., 202
 Rose, J. C., 35, 109
 Rosecan, M., 19
 Rosen, I., 79
 Rosenbaum, J. D., 142
 Rosenblum, R., 30
 Rosenthal, N., 101
 Rosenthal, R. L., 101
 Ross, J. F., 92, 121
 Roth, K. L., 29, 96
 Rothechild, I., 16
 Rotter, R., 51
 Rowe, G. G., 11
 Roy, A. M., 44
 Rubin, A. L., 136
 Rubini, M. E., 45, 48, 138

- Rucknagel, D. L., 67, 93
 Rudolph, L. A., 113
 Ruegamer, W. R., 127
 Ruskin, A., 69
 Ryan, J. M., 197
 Ryan, R. J., 144
 Rytand, D. A., 53

 Said, S., 196
 St. Marc, J. R., 73
 Sala, G., 148
 Samet, P., 114
 Samuels, A. J., 99
 Samuels, L. T., 148
 Sandberg, H., 73
 Sapin, S., 35, 108
 Sarnoff, S. J., 35, 96
 Saslaw, S. M., 77
 Saunders, R. H., Jr., 98
 Savory, P. B., 18
 Saxton, G. A., Jr., 25, 145
 Schaaf, M., 76
 Schack, J., 38
 Scherlis, S., 32, 111
 Schieve, J. F., 210
 Schilling, R. F., 195
 Shimert, G., 111
 Schittone, M. T., 28
 Schneider, E. M., 78, 132, 153, 206
 Schneiderman, M. A., 30
 Schoenberger, J., 204
 Schoolman, H. M., 100
 Schottstaedt, W. W., 74
 Schreier, A., 108
 Schreiner, G. E., 47, 148
 Schroeder, H. A., 1
 Schultz, A., 120
 Schulz, E. G., 9
 Schwartz, H., 51
 Schwartz, S. O., 100
 Schwartz, T. B., 76
 Schwartz, W. B., 44
 Schwarz, K., 19
 Scotti, T. M., 34
 Scribner, B. H., 58
 Segal, M. A., 208
 Seldin, D. W., 76, 126, 135, 136
 Seltzer, H. S., 201, 203
 Sensenbach, W., 25
 Shackman, N. H., 119
 Shapiro, A. P., 117
 Sheldon, M. B., 197
 Shellenberg, R., 31
 Shelton, E. K., 124, 125
 Sherlock, S. P. V., 48
 Sherry, S., 200
 Sherwin, R., 33
 Shipmand, M. E., 142

 Shively, J. A., 18
 Shmagranoff, G. L., 200
 Shock, N. W., 105, 134
 Shreeve, W. W., 64, 138
 Shuman, C. R., 123
 Sieker, H. O., 71, 81, 147
 Silver, H. M., 146
 Silverman, F. R., 127
 Singh, B. P., 63
 Siperstein, E., 42
 Sise, H. S., 103
 Skeels, R. F., 124, 125
 Skilman, T. B., 203
 Slobody, L., 140
 Smith, H. W., 22, 205
 Smith, R. E., 13
 Soloff, L. A., 34, 106
 Sommers, B., 10
 Spaet, T. H., 51, 52
 Spencer, G. N., 211
 Spencer, R. P., 61
 Spurr, C. L., 14, 15, 122
 Spurrier, W., 100
 Squires, R. D., 127
 Starr, P., 57, 61
 Stauffenberg, R., 29
 Stauffer, H. M., 34, 106, 107
 Stead, W. W., 24
 Steblay, R. W., 211
 Steele, J. M., 40
 Steiger, W. A., 29
 Steinbach, H. L., 55
 Steinberg, D., 112
 Sterling, K., 120
 Sternleib, R. O., 207
 Steyermark, P., 124
 Stiles, W., 197
 Stohlman, F., Jr., 30, 96
 Stollerman, G. H., 118, 119
 Stolloff, I. L., 134
 Stone, C. A., 204
 Stone, J. L., 113
 Stone, R. W., 49
 Storey, C. F., 115
 Story, P., 94
 Stover, J. W., 14
 Strang, R., 140
 Streeten, D. H. P., 131, 201
 Streitfeld, M. M., 77
 Stribling, S. H., 14, 15, 122
 Stuckey, J., 105
 Stults, R., 202
 Suhrland, L. G., 97
 Summerskill, W. H. J., 48
 Sun, L. S. Y., 102
 Sweet, N. J., 62

 Sydnor, K. L., 16
 Szanto, P. B., 100

 Talbert, P. C., 18
 Talbot, T. R., Jr., 8
 Talmers, F. N., 120
 Tang, J., 119
 Tangco, F., 40
 Taranta, A., 118
 Tatge, W. A., 211
 Tauzin, M., 57
 Teng, H. C., 126
 Texter, E. C., Jr., 22, 205
 Thomas, H. D., 70
 Thomas, W. A., 199
 Thorn, G. W., 73
 Thorne, C. B., 68
 Threefoot, S. A., 75
 Tobian, L., 199
 Tobias, C. A., 130
 Tokuyasu, K., 65
 Tomizawa, H. H., 58
 Toporek, M., 194
 Towery, B. D., 133
 Tremblay, G., 124
 Tyler, F. H., 59

 Ulrich, R. A., 63
 Ultmann, J. E., 102
 Underwood, V., 119

 Valentine, R. J., 61
 Valero, A., 104
 Vanamee, P., 104, 126
 VanArsdel, P., Jr., 58
 Varela, J. E., 52
 Vaughan, J. H., 67
 Victor, M., 38
 Vitale, J. J., 130
 Vogel, W., 120
 Volwiler, W., 104

 Waife, S. O., 50
 Waldron, J. M., 45
 Waldstein, S. S., 141
 Walker, I. C., 197
 Walker, W. J., 106
 Wall, R. L., 102
 Waller, J. J., Jr., 15, 122
 Walser, M., 36, 126
 Walsh, W. P., 36
 Ward, J. R., 144
 Warner, G. F., 55
 Warren, J. V., 82, 136
 Watkin, D. M., 134
 Watson, J. R., 146
 Watson, R. J., 28
 Weaver, D. H., 113
 Webster, G. D., Jr., 124
 Weigert, H. T., 58
 Weil, M. H., 194

 Weiner, L., 28
 Weinstein, A. B., 11
 Weinstein, H. G., 19
 Weinstein, I. M., 52
 Weisman, R., Jr., 6, 7
 Weitzner, H. A., 59
 Welch, G. E., 79
 Welsh, G. W., 122
 Welt, L. G., 68
 Wenk, E. J., 140
 Wertheimer, L., 40
 Whipple, G. H., 109
 White, J. E., 76
 White, L. P., 48
 Wilkerson, V., 31
 Wilkins, R. W., 117
 Willardson, D. G., 137
 Willett, R. W., 80
 Williams, A. D., 101
 Williams, E. H., Jr., 77
 Williams, J. D., 144, 204
 Williams, M. H., Jr., 49
 Williams, R. H., 58, 122
 Williams, T. F., 68, 142
 Williams, W., 28
 Willis, P. W., III, 196
 Wilson, J. D., 135
 Wilson, R. H., 24, 81, 206
 Wilson, W. S., 196
 Wiltshaw, E., 30, 98
 Wiltzie, D. S., 200
 Winchell, P., 198
 Winnik, D. E., 211
 Winzler, R. J., 101
 Wohl, M. G., 123
 Wohltmann, H., 199
 Wolf, S., 132
 Wolff, H. G., 128
 Wolfson, W. Q., 201
 Wood, J. E., 117
 Woodward, W., 202
 Wotiz, H. H., 123
 Wright, D. U., 31
 Wroblewski, F., 20, 37, 48, 49, 112, 119
 Wu, N., 81, 145
 Wyngaarden, J. B., 46

 Yakulis, V. J., 207
 Yielding, K. L., 72, 118
 Yonemoto, R. H., 95
 Young, A. C., 146
 Young, I. I., 201
 Young, L., 105

 Zamcheck, N., 130
 Zafanotis, C. J. D., 46
 Zatuchni, J., 34, 106
 Zieve, L., 120
 Zimmerman, H. J., 19

SUBJECT INDEX

- Acid-base balance**
in pregnancy, 63
and rubidium and potassium, 44
- Acid secretion** into gastric juice, 205
- Acidosis**
chronic
Diamox in, 147
and kidney function, 136
diabetic, treatment of, 203
hyperchloremic, following ureterosigmoidostomy, 126
metabolic, cardiovascular alterations in, 104
- Acromegaly**, kidney in, 13
- ACTH**
and bilirubin metabolism, 141
and chromatophore number, 73
and estrogen excretion, 73
and gastric secretion, 131
-gel and adrenal cortex, 201
intermittent use of, 201
in nephrotic syndrome, 17
in rheumatic fever, 12
- Adrenal cortex**
and ACTH-gel, 201
and corticoid therapy, 201
- Adrenalectomy**, and renal function, 135
- Adrenal-gastric relationship**, 131
- Agammaglobulinemia**, acquired, with hypersplenism, 8
- Age**, and circulation, 105
- Agglutinins**
cold, due to *Listeria monocytogenes*, 207
leukocyte, 31, 51, 99
- Alcaptonuria**, inheritance of, 129
- Alcoholism**, Meratran for, 149
- Aldosterone**
bioassay for, 124
isolation of, 124
- Alkaline phosphatase**, as index of hepatocellular integrity, 20
- Allergy**, 27-28
skin testing in, 119
See also Collagen diseases and allergy
- Alveolar-arterial gas tension**, in acute poliomyelitis, 25
- American Federation for Clinical Research**, history of, 151
- Aminometramide**, effects of, 211
- Aminophylline**, evaluation of, 207
- Ammonia production**, role of, 76
- Ammonium**, in liver disease, 48, 142
- Anasarca**, various, digitalis in, 69
- Anemia**
dilution, erythropoiesis in, 94
and glomerular filtration and renal vascular tone, 210
and hemoglobin, 6
and hemolysis in hemoglobinuria, 7
hemolytic
antibody characteristics in, 67
heparin in, 96
red cells agglutinated in, 29
scintillation counting in, 195
iron turnover in, 91
megaloblastic
cobaltous chloride in, 194
in pregnancy, 6
microcytic hypochromic, erythropoiesis in, 95
pernicious
B₁₂ in, 7
due to B₁₂ deficiency, 28
citrovorum factor for, 97
erythropoiesis and iron movement in, 92
therapy without intrinsic factor, 28
reticulocyte response in, 94
sickle cell
diagnosis of, 96
hyposthenuria in, 29
in pregnancy, 6
transfusions in, 29
splenic, 94
- Anesthesia**, and carbohydrate metabolism, 202
- Angina pectoris**, sinus graft operation for, 11
- Angiocardiography**, and circulation time, 106
- Anorexia**, and methylphenyl isopropylamine sulfate, 128
- Anoxia**, and potassium transport, 111
- Anoxemia test**, for coronary artery disease, 33
- Ansolysen**, for hypertension, 116
- Antibody**
in hemolytic anemia, 67
to tuberculopolysaccharide and tuberculoalbumin, 27
- Anticholinergic drug**, a new, 22
- Antidiuretics**, in edema, 138
- Antihemophilic globulin**, depression of, 52
- Antistreptolysin-O index**, for large samples, 77
- Anuria**, extension of life in, 47
- Arrhythmias**, auricular, CR leads in, 39
- Arteriosclerosis**, blood pressure in, 115
- Artery disease**, coronary, serum lipid in, 15
- Aschoff bodies**, in mitral stenosis, 34
- Atrophy**, adrenal, in Cushing's syndrome, 43
- Azaserine**, and tryptophane metabolism, 21
- BAL**, and peripheral neuropathy, 80
- Ballistocardiogram**
in congenital heart disease, 54
affected by occluding inflow and outflow, 70
- Ballistocardiography**, in mitral valve disease, 70
- Basophil count**, absolute, in health and disease, 31
- Bentyl**, and peripheral circulation, 199
- Bilirubin**
metabolism, and ACTH, 141
output, total, 196
- Biopsy**
of kidney, 209
of liver, 78
- BL700B**, evaluation of, 22
- Block**, right intraventricular, 196
- Blood**, 6-10, 28-32, 51-53, 67-68, 91-104, 194-196
electrolytes, insulin effect on, 59
flow
in denervated limbs, 40
measurement of, 40
retinal, 71
and volume, 54
and inositol, 127
levels, in hepatic disease, 19
lipids, and temperature, 45
and low potassium diet, 127
pressure
in arteriosclerosis, 115
and behavioral disturbances, 117
and Rauwolfia and Reserpine, 197
transfusions
in sickle cell anemia, 29
tuberculin distribution in, 133
vessels, studies of, 145
volume
and flow, 54
in Laennec's cirrhosis, 143
pulmonary, 110
and reticulocyte response, 94
- Blood cell(s)**
peripheral, alkaline phosphatase activity in, 98
- red**
agglutinated in hemolytic anemia, 29
damage and Cr⁵¹, 30
destruction of, 52, 95
fragility in hemolytic anemia, 8
mass, in heart failure, 114
osmometric behavior of, 68
prevention of hemolysis of, 8
production of, 52
splanchnic volume of, 37
See also Erythropoiesis
- white**
agglutinins, 31, 51, 99
and alkaline phosphatase activity, 30, 98
and LE factor and quinacrine, 98
survival in polycythemia vera, 97
- Body fluids**, in heart failure and hypertension, 35
- Brain**, foodstuff of, 56
- Breathing**, 100% oxygen and pressure, 146
- Bromsulfalein clearance**
in normalcy, 19
effect of increased infusion rate, 141

- Bronchiectasis**, pulmonary function in, 49
Bronchodilators, evaluation of, 25, 207
Bronchspirometry, during thoracic surgery, 24
Buergher's exercises, in occlusive arterial disease, 200
Bundle branch block, vector analysis of, 39, 108
Burn, and protein anabolism, 127
Calcinuria, neuromuscular activity in, 144
Calcium
 concentration, and carbon dioxide, 204
 disodium ethylenediamine tetraacetate, and lead intoxication, 80
 retention, and osteoporosis, 76
Calories, supplementary, in chronic liver disease, 142
Cancer, breast, hypophysectomy in, 200
Carbohydrate
 index, in assessing hepatic function, 141
 metabolism, and anesthesia, 202
Carbon dioxide
 and calcium concentration, 204
 mixed venous, 145
Cardiac output
 and resistance, 69
 and thermal trauma, 54
Cardiovascular system, 10-12, 32-40, 53-56, 69-72, 104-118, 196-200
Cation exchange resins, for Laennec's cirrhosis, 18
Central nervous system, 40-41, 56-57, 72
Chloride
 cobaltous, in hypoplasia and megaloblastic anemia, 194
 in gastrointestinal tract, 62
Chlorpromazine
 -induced water diuresis, 138
 and jaundice, 23
 and surgery, 212
Cholecystectomy, biopsies in, 18
Cholecystitis, and biliary inflammation, 18
Cholinesterase
 as index of hepatocellular integrity, 20
 -inhibiting drug, 144
Christmas disease, acquired, 103
Chromatophore number, and ACTH, 73
Circulation
 and age, 105
 extracorporeal, 105
 and hyperthyroidism, 120
 intracardiac, angiocardigraphy in, 106
 lesser, hematocrit of, 110
 peripheral, and Bentlyl, 199
 pulmonary, vasoconstriction in, 35
Cirrhosis
 and hypertension, 143
 Laennec's
 blood volume in, 143
 Diamox, cation exchange resins and cortisone for, 18
 hemodynamic lesion in, 65
 water loads in, 142
Citrovorum factor, for pernicious anemia, 97
Clearance
 Bromsulfalein, 19
 plasma
 hepatocellular, 141
 iron, 91
 renal, of 18 amino acids, 64
Coagulation time, effect of fat on, 68
Coarctation of aorta, flush technic in, 199
Coccidioidomycosis
 drug therapy of, 78
 spherules in, 77, 134
Cold, and mechanism of esophagus, 130
Collagen diseases and allergy, 12-13, 72, 118-120
Commissurotomy, mitral, dyspnea after, 34
Compound B, and gastric secretion, 131
Concentration, bone sodium, and sodium loading, 125
Congestion, pulmonary, Valsalva maneuver in, 115
Cor pulmonale, complicating left ventricular failure, 33
Corticosteroids
 bioassay for, 124
 and neoplastic disease and stress, 42
Corticosterone, and gastric secretion, 131
Cortisone
 "diuresis," 14
 in hemolytic anemia, 8
 and hypothyroidism, 61
 for Laennec's cirrhosis, 18
 in peritonitis, 208
Cough, circulatory effects of, 82
CR leads, in diagnosis, 39
Cryofibrinogen, identification of, 20
Cryoglobulinemia, studies of, 104
Cushing's syndrome, compensatory adrenal atrophy in, 43
Dead space, pulmonary, studies on, 206
Depression, Meratram for, 41
Dextran, hemostatic defect with, 103
Diabetes
 I¹³¹-labeled insulin in, 122
 mellitus
 and fructose feeding, 203
 and hypoglycemia, 203
 test for, 122
 Sorbitol in, 123
Diamox
 in chronic acidosis, 147
 and electrolytes, 43
 and gastric secretion, 205
 for Laennec's cirrhosis, 18
 during pregnancy, 63
 in pulmonary emphysema, 147
Digitalis
 and potassium transport, 111
 in various anasarca, 69
Digoxin, in experimental failure, 114
Diodrast, Tm, and TmPAH, 134
Diuresis
 and ethyl alcohol, 44
 mercurial, and sodium excretion, 44
 water
 chlorpromazine-induced, 138
 sustained, 138
 in hypertension, 117
 sulfate, and acid and electrolyte excretion, 48
Diuretics, mercurial, and kidney succinic dehydrogenase, 210
Drugs, antipressor, clinical evaluation of, 21
Dyspnea, after mitral commissurotomy, 34
Dystrophy, muscular
 determination of muscle mass in, 144
 lean body determinations in, 76
 neutron activation of tissue in, 204
 urinary pentose in, 59
Edema, antidiuretics in, 138
Effusions, pleural and pericardial, hydrocortisone for, 148
Einthoven hypothesis, discrepancies of, 12
Electrocardiogram(s)
 and acute magnesium depletion, 106
 in hyperchloremic acidosis, 125
 in hypothermia and circulatory occlusion, 107
 insulin effect on, 59
 in liver disease, 142
 and potassium transport, 111
Electrocardiography, of acute ischemia, 38
Electrokymography, in mitral valve lesions, 12
Electrolytes
 of arterial wall, 199
 and Diamox, 43
Electrophoresis
 of cryo- and macroglobulinemia, 104
 in Hodgkin's disease, 102
 of synovial fluid, 72, 118
Emotion, and renal excretion, 74
Emphysema
 breathing in, 146
 intrapulmonary gas mixing in, 66
 lung volume and gas mixing in, 147
 and 99.6% oxygen breathing, 81
 pulmonary
 Diamox in, 147
 respiratory mechanics in, 147
Encephalopathy, Wernicke's, circulatory studies in, 38
Endocrines and Metabolism, 13-17, 41-46, 57-62, 73-77, 120-130, 200-205
Endometrium, growth characteristics of, 62

- Epinephrine**
evaluation of, 207
and ventricular contraction, 70
Erythrocytes, *see* Blood cells, red
Erythropoiesis
in dilution anemia, 94
and ferrokinetic patterns, 91
in microcytic hypochromic anemia, 95
in pernicious anemia, 92
Esophagus, motor mechanism of, 130
Estrogen excretion, and ACTH, 73
Ethyl alcohol
and diuresis, 44
and the liver, 206
Excretion, acid and electrolyte, during sulfate diuresis, 48
Exercise
in mitral stenosis, 35
tolerance test, in heart disease, 32
Expiratory flow curve, and maximum breathing capacity, 81
Fat
and coagulation time, 68
emulsion, and bilirubin output, 196
removal, and heparin, 17
Ferrocyanide, as measure of extracellular fluid, 45
Fertility, and inositol, 127
Fever, vascular alterations in, 104
Fibrillation, atrial, and mitral insufficiency, 110
Fluid
extracellular, measure of, 45
synovial, electrophoretic analysis of, 72, 118
Flush technic, in diagnosis of coarctation of aorta, 199
Flutter
atrial, and atrial rate, 53
auricular, study of, 53
Food drive, 74
Fructose
feeding, in diabetes mellitus, 203
infusions, and lactic acid production, 204
Gas mixing
in emphysema, heart failure and obesity, 147
intrapulmonary, and body position, 81
Gastrectomy, subtotal, hematologic effects of, 67
Gastric *see* Stomach
Gastrointestinal system, 62, 130-132, 205-207
Genetics, 187
Genital organs, 62
Glands, adrenocortical, and thyroid hormone, 121
Glomerular
filtration, and anemia and polycythemia, 210
membrane, studies of, 211
Glucose
for diabetic acidosis, 203
insulin tolerance test, effect of disease on, 15
tolerance test, effect of disease on, 15
Graft operation, for angina pectoris, 11
Growth, and inositol, 127
Headache, and hydration, 128
Heart
disease
anoxemia test in, 33
congenital
ballistocardiography in, 54
and pulmonary artery occlusion, 198
vectorcardiography in, 108
detection of, 32
familial, 10
neurogenic factors in, 32, 111
and Einthoven hypothesis, 12
failure
body fluids in, 36
congestive
hexamethonium for, 49
and pulsus alternans, 10
serum cholesterol in, 11
TEAC in, 198
and cor pulmonale, 33
and dyspnea after mitral commissurotomy, 34
experimental, 114
intravascular volume in, 114
lung volume and gas mixing in, 147
nitroglycerine for, 113
plasma volume and red cell mass in, 114
rubidium and potassium excretion in, 75
tilting in, 197
tissue metabolism in, 34
function, demonstrated, 107
structure, demonstrated, 107
Hematocrit
of lesser circulation, 110
pulmonary, and pulmonary volume, 110
in spherocytosis, 95
splanchic, 37
Hemodynamics
of mitral stenosis, 11
of shock infection, 10
Hemoglobin
in anemia, 6
C disease, 9
G, a fifth abnormal, 51
H, a new abnormal, 93
new inherited abnormality of, 67
Hemoglobinuria, paroxysmal nocturnal, hemolysis in, 7
Hemolysis
in hemoglobinuria, 7
measure of, 196
prevention of, 8
Hemolytic
disease of newborn, 7, 52
syndrome, prosthesis in, 96
system, in acute leukemia, 100
Hemophilia
B, acquired, 103
female, 53
Hemorrhage, in acute leukemia, 101
Hemostasis, and Dextran, 103
Heparin
and fat removal, 17
in hemolytic anemias, 96
Hexamethonium
in congestive heart failure, 49
and resistance, 115
Hepatic *see* Liver
Histoplasmosis
and lymphoma, 208
organisms found in, 208
Hodgkin's disease, electrophoresis in, 102
Hormones, steroid, effect on tissue growth, 80
Host factors, and infection, 154
Hydralazine, for hypertension, 2
Hydration, and headache, 128
Hydrocortisone
and gastric secretion, 131
metabolic effects of, 16
for pleural and pericardial effusions, 148
tissue binding of, 16
Hyperchloremia, mechanism of development of, 136
Hyperchlorhydria, and reserpine, 206
Hyperemia, reactive, mechanism of, 117
Hyperreflexia, autonomic, 56, 143
Hypersplenism, with acquired agammaglobulinemia, 8
Hypertension
Ansölysen for, 116
body fluids in, 36
and cirrhosis, 143
drug therapy of, 1
Rescinnamine for, 71
Rauwolfia and Reserpine in, 197
reserpine for, 71
serum magnesium and plasma sodium in, 116
water diuresis and Pitressin antidiuresis in, 117
Hyperthyroidism
and circulation, 120
and I¹³¹ therapy, 121
serum lipid in, 15
Hypertrophy
CR leads in, 39
vectorcardiographic diagnosis of, 109
Hyperuricemia, phosphaturic agents in, 135
Hypofibrinogenemia, in acute leukemia, 101
Hypoglycemia
and diabetes mellitus, 203
insulin-induced, 59, 75
Hypophysectomy, in breast cancer, 200
Hypophysis, proton irradiation of, 130
Hyposthenuria, in sickle cell anemia, 29
Hypotension, and Rauwolfia, 55
Hypothermia, electrocardiogram in, 107
Hypothyroidism
and cortisone, 61
serum lipid in, 15
thyrotropin for, 14
Hypoventilation, alveolar, in polycythemia, 31

- Hypoxia**, and 99.6% oxygen breathing, 81
- I¹³¹**
- labeled insulin in diabetes, 122
 - labelled tuberculin, distribution of, 27, 133
 - protein-bound, 120
 - therapy, and hyperthyroidism, 121
 - uptake, 73
- Infarction**, splenic, in sickle cell disease, 51
- see* Myocardial infarction
- Infection**
- and host factors, 154
 - shock due to, 10
 - streptococcal, and Sydenham's chorea, 118
- Infectious diseases and antibiotics**, 46-47, 77-78, 132-134, 207-209
- Inhibition, gastric**, agents for, 132
- Inositol**, and hemopoiesis, growth and fertility, 127
- Insufficiency**
- mitral, and atrial fibrillation, 110
 - pulmonary
 - analyzed, 145
 - CO₂ administration in, 25
 - and tracheotomy, 146
- Insulin**
- and blood electrolytes and electrocardiogram, 59
 - increasing sensitivity of, 59
 - I¹³¹-labeled, 122
 - insufficiency, 58
- Intrinsic factor**
- assay for, 28
 - and binding power, 194
 - omitted in pernicious anemia therapy, 28
- Iodine**, in thyrotoxicosis, 42
- Iron**
- binding, in abnormal sera, 93
 - excretion, factors controlling, 92
 - movement, in pernicious anemia, 92
 - storage and ferrokinetic patterns, 91
 - turnover, in anemia and normalemia, 91
- Irradiation proton**, of hypophysis, 130
- see also* X-ray
- Ischemia**
- acute, electrocardiography in, 38
 - CR leads in, 39
- Jaundice**, and chlorpromazine, 23
- JB 323**, evaluation of, 22
- Ketel method**, modified, 58
- Ketosteroid secretion** in tuberculosis, 133
- Kidney**, 17-18, 47-48, 63-64, 134-140, 209-211
- in acromegaly, 13
 - and anemia and polycythemia, 210
 - artificial, 17
 - biopsy studies of, 209
 - in lupus erythematosus, 13
 - in carbon tetrachloride poisoning, 47
 - and chronic acidosis, 136
 - disease, oxygen consumption in, 18
 - function
 - and adrenalectomy, 135
 - in acute necrosis, 137
 - and emotions, 74
 - and insulin hypoglycemia, 75
 - Hg distribution in, 135
 - in hyperuricemia, 135
 - in sickle cell disease, 97
 - succinic dehydrogenase, and mercurial diuretics, 210
 - and triiodothyronine and thyroxine, 14
- Kinetocardiography**, in mitral valve disease, 70
- Lactic acid**, production, 204
- Lead**
- intoxication, and calcium disodium ethylenediamine tetra-acetate, 80
 - poisoning, childhood, 22
- LE cell**, and leukocytes, 98
- Lesions**
- glomerular, in toxemia of pregnancy, 209
 - mitral, electrokymography in, 72
- Leukemia**
- acute
 - fibrinolytic purpura in, 9
 - hemolytic system in, 100
 - hemorrhage in, 101
 - AKR, transplantation of, 100
 - drug therapy for, 101
 - human and AKR, 100
 - longevity of, 99
 - onset of, 99
- Leukocytes** *see* Blood cells, white
- Listeria monocytogenes**, cold agglutinins due to, 207
- Liver (and biliary tract)**, 18-20, 48-49, 65, 78-79, 141-143
- biopsy of, 78
 - degeneration, C¹⁴-acetate in, 19
 - disease
 - ammonium transport in, 48
 - blood "ammonia" levels in, 19
 - chronic
 - and methyltestosterone, 141
 - supplementary calories in, 142
 - plasma electrolytes, electrocardiographic changes and ammonium in, 142
 - serum transaminase in, 48, 49
 - and ethyl alcohol, 206
 - function, carbohydrate index in, 141
 - and pressure measurements, 79
 - and tetracycline, 132
- Lung**
- disease
 - and hypometabolism, 82
 - and maximum expiratory curve, 146
 - distention and morphology, 24
 - function, and hexamethonium, 115
 - nodules, organisms found in, 208
 - volume
 - and body position, 81
 - in emphysema, heart failure and obesity, 147
 - see also* Pulmonary
- Lupus erythematosus disseminatus**, kidney biopsy in, 13
- Lupus nephritis**, natural history of, 139
- Lymph**
- node imprints, cytologic study of, 102
 - thoracic duct, 65
- Lymphatic system**, 65
- Lymphocyte**, flow in thoracic duct lymph, 65
- Lymphoma**, and histoplasmosis, 208
- Macroglobulinemia**, studies of, 104
- Magnesium depletion**, acute, electrocardiogram in, 106
- Marrow**, damage, and Rh antibody, 52
- hypoplasia, cobaltous chloride in, 194
 - radiography of, 55
- Maximum breathing capacity**, and rapid expiration flow curve, 81
- Maximum expiratory curve**, use of, 146
- Meratran**
- for alcoholism, 149
 - for depression, 41
 - for obesity, 40
- Mercaptomerin**
- clinical evaluation of, 55
 - renal distribution of Hg²⁺, tagged, 135
- Mercaptopurine**
- and leukemic tissue, 79
 - metabolic and cytochemical effects of, 101
 - and tryptophane metabolism, 21
- Metabolism**
- and hydrocortisone, 16
 - and mercaptopurine, 101
 - and nortestosterone cyclopentylpropionate, 60
 - and proton irradiation, 130
 - reduced, in lung disease, 82
 - and stress, 73
 - and testosterone propionate, 60
 - and tetracycline, 132
 - tissue, in heart failure, 34
 - uric acid, and phenylbutazone, 46
 - see also* Endocrines and metabolism
- Methods, laboratory**, 63, 145
- Methylphenyl isopropylamine sulfate**, an anorexigenic compound, 128
- Methyltestosterone**, and chronic liver disease, 141
- Mucosa, gastric**, succinic oxidase activity of, 130
- Muscle mass**, determination of, 144
- Myocardial infarction**
- C-reactive protein in, 112
 - experimental, 69
 - potassium transport in, 37
 - serum transamination in, 37, 112-113
- Myxedema**, triiodothyronine in, 41
- Necrosis, acute**, kidney function in, 137

- Neodrol**, evaluation of, 60
Neoplasm, lung, cryofibrinogen in, 20
Neoplastic disease, 20-21, 79-80 and corticosteroids, 42 tryptophan in, 201
Nephrotic syndrome, ACTH in, 17 classification of, 139 remissions in, 140 with renal vein thrombosis, 139 serum albumin in, 64 steroid therapy of, 140
Nervous system and muscle, 143-145
Neuropathy, peripheral, and BAL, 80
Neurosis, experimental, and blood pressure, 117
Nitrite, and kinetocardiography and ballistocardiography, 70
Nitroglycerine, for left ventricular failure, 113
Nortestosterone cyclopentylpropionate, evaluation of, 60
Norepinephrine and electrolytes of arterial wall, 199 and ventricular contraction, 70
Obesity lung volume and gas mixing in, 147 Meratran for, 40 polycythemia of, 194 and satiety mechanism, 74
Occlusion circulatory, electrocardiogram in, 107 pulmonary, in congestive failure, 198
Osteoporosis, and calcium retention, 76
Ovulation, and progesterone, 16
Oxygen consumption, in renal disease, 18
Oxytetracycline, in peritonitis, 208
Pain insensitivity to, 72 in peptic ulcer, 153
Para-aminosalicylate potassium, 46 for pulmonary tuberculosis, 133
Penicillin, and group A streptococci, 132
Pentose, in muscular dystrophy, 59
Pepsinogen secretion, into gastric juice, 205
Peptic Disease, chronic, 85
Pericarditis, idiopathic, 105
Peripheral arterial disease, measurement of blood flow in, 40
Peripheral nervous system, 72
Peritonitis, cortisone and oxytetracycline for, 208
Pharmacology and toxicology, 21-23, 80-81
Phenylbutazone, and uric acid metabolism, 46
Pheochromocytoma, diagnosis of, 36
Phlebography, intraosseous, 55
Phonocardiography, selective, 196
Phosphatase activity factors influencing, 30 in peripheral blood cells, 98
Pitressin antidiuresis, in hypertension, 117
Plasma electrolytes in hyperchloremic acidosis, 126 in liver disease, 142 lipids, and Squalene, 45 sodium and hypertension, 116 thromboplastin component deficiency, acquired, 103 volume, in heart failure, 114
Platelet survival, in thrombocytopenia, 102
Poisoning carbon tetrachloride, 47 salicylate, therapy for, 148
Poliomyelitis, acute, alveolar-arterial gas in, 25
Polycythemia with alveolar hypoventilation, 31 and glomerular filtration and renal vascular tone, 210 of obesity, 194 vera, leukocyte survival in, 97
Polydipsia, in cortisone "diuresis," 14
Posture, and sodium excretion, 136
Potassium and acid-base balance, 44 depletion, indices of, 61 diet, low, and urine and blood, 127 excretion, with and without congestive failure, 75 fecal, and adrenal steroids, 124 transport in heart, 111 in the myocardium, 37
Pregnancy acid-base balance in, 63 anemia in, 6
Pressure hepatic venule, 79 left heart, in mitral stenosis, 35 pulmonary artery, across capillary bed, 24 retinal, 71
Progesterone, and ovulation, 16
Propylthiouracil, extrathyroidal effects of, 58
Prosthesis, in hemolytic syndrome, 96
Protein anabolism, and burns, 127 c-reactive in myocardial infarction, 112 and surgical trauma and rheumatism, 119 gastric secretory effects of, 62
Prothrombin analysis, two-stage, 32, 103
Protoveratrine, for hypertension, 2
Pulmonary efficiency, nitrogen and helium in, 65 function, in bronchiectasis, 49
Pulsus alternans, and congestive heart failure, 10
Purpura, fibrinolytic, in acute leukemia, 9
Pyroxidine activity, 21
Quinacrine, and leukocytes, 98
Quinidine, metabolic effect of, 75
Radiolodine *see* I¹³¹
Radiosulfate and edema, 126 space, in disease, 126
Rauwolfia for hypertension, 197 hypotensive mechanisms in, 55
Reagin, atopic, coprecipitation of, 13
Renal, *see* **Kidney**
Rescinnamine, for hypertension, 71
Reserpine and gastric secretion, 131 hyperchlorhydria of, 206 for hypertension, 1, 71, 197 in schizophrenia, 57
Respiratory system, 24-26, 49, 65-66, 81-83, 145-148
Reticulocyte response, in anemia, 94
Rh antibody, in hemolytic disease of newborn, 52
Rheumatic fever ACTH for, 12 serum transaminase in, 119
Rheumatism, and c-reactive protein, 119
Roentgenology, 148 *see also* X-ray
Rubidium and acid-base balance, 44 excretion, with and without congestive failure, 75
Schizophrenia, and reserpine, 57
Scintillation counting, and hemolytic anemia, 195
Secretion gastric and ACTH, hydrocortisone and corticosterone, 131 and reserpine, 131 hydrochloric acid, 130
Septal defect, atrial, past middle age, 107
Serum albumin turnover in nephrotic syndrome, 64 cholesterol and brain extract, 128 in congestive heart failure, 11 citric acid, in uremia, 137 C-reactive protein, significance of, 63 iron, in hemolytic disease of newborn, 7 lipid, in hypothyroidism, hyperthyroidism and coronary artery disease magnesium, in hypertension, 116 mucoprotein, physiology of, 129 potassium, determination of, 58 transaminase activity, observations in a large group, 200 as index of hepatocellular integrity, 20 in liver disease, 48, 49

- Serum** (*Cont'd*)
 in myocardial infarction, 37, 112-113
 in rheumatic fever, 119
Shock, hemodynamics of, 10
Sickle cell(s)
 anemia vs. trait, 96
 disease, kidney in, 97
 trait, in pulmonary tuberculosis, 30
see also Anemia, sickle cell
Sicklelema, and splenic infarction, 51
Sin throm, evaluation of, 196
Skin, 66
 test for allergy, 119
Sodium
 dextro-thyroxine pentahydrate, and thyroid hormone, 57
 excretion
 and mercurial diuresis, 44
 posture and neck compression in, 136
 loading, and bone sodium concentration, 125
 splanchnic exchangeable, 125
Sorbitol, for diabetes, 123
Space, radiosulfate, in disease, 126
Sperm, mineral and water composition of, 46
Spherocytosis
 carriers of heredity, 195
 trapped plasma in hematocrits in, 95
Spinal cord injury, and autonomic hyperreflexia, 56, 143
Spleen, traumatic rupture of, 50
Squalene, and plasma lipids, 45
Statistics, 185
Stenosis
 mitral
 Aschoff bodies in, 34
 exercise in, 35
 hemodynamics of, 11
 left heart pressure in, 35
 pulmonary alveolar membrane in, 24
 pulmonic, mild isolated, 107
Steroid(s)
 adrenal, and fecal potassium, 124
 aldosterone, isolation of, 124
 ketogenic, determination of, 202
 11-oxygenated-17-ketogenic, determined, 123
 therapy, in nephrotic syndrome, 140
Stomach
 and adrenocortical function, 131
 secretions in, 205
 effect of Diamox on, 205
Streptococcus, group A, and penicillin, 132
see also Infection
- Stress**
 and corticosteroids, 42
 and physiology, 128
Succinic dehydrogenase activity, of tuberculous tissue, 77
Succinic oxidase activity, of gastric mucosa, 130
Surgery
 and Chlorpromazine, 212
 and c-reactive protein, 119
 thoracic, bronchspirometry in, 24
Sydenham's chorea, and streptococcal infection, 118
Syncope, 82
Synovial fluid, electrophoretic analysis of, 118
- Temperature**, and blood lipids, 45
Testosterone
 phenylacetate, clinical experience with, 124
 propionate, metabolic effects of, 60
Tetany, and CO₂ depletion, 82
Tetracycline, metabolic and hepatic effects of, 132
Tetraethyl ammonium chloride
 in congestive failure, 198
 and intravascular volume, 114
Tetralogy of Fallot, acyanotic, 198
Therapeutics, 148-149, 211-212
Thrombocytopenia, platelet survival in, 102
Thrombophlebitis migrans, cryofibrinogen in, 20
Thrombosis, renal vein, with nephrotic syndrome, 139
Thyroid
 and adrenocortical function, 121
 function, and I¹³¹ concentration, 73
 hormone
 degradation of, 120
 production and utilization of, 42
 studies on, 57
 secretion, in thyrotoxicosis, 42
Thyrotoxicosis, thyroid secretion in, 41
Thyrotropin, for hypothyroidism with goiter, 14
Thyroxine, and kidney function, 14
Tissue
 binding, of hydrocortisone, 16
 growth, and steroid hormones, 80
 leukemic, and mercaptopurine, 79
 neutron activation of, 204
 tuberculous, 77
Tm PAH, and Tm Diodrast, 134
Toxemia of pregnancy, glomerular lesions in, 209
Tracheotomy, and pulmonary insufficiency, 146
- Transfusion**, in thermal trauma, 93
Trauma, thermal, transfusion in, 93
Trichophyton tonsurans, 66
Trilodothyronine
 and kidney function, 14
 in myxedema, 41
Tryptophane metabolism, 21, 201
Tubercle bacilli, rapid culture of, 47
Tuberculin, distribution in blood, 133
Tuberculosis, pulmonary
 17-ketosteroid excretion in, 133
 paraaminosalicylic acid for, 133
 sickle cell trait in, 30
- Ulcer**, peptic, pain in, 153
Uremia
 artificial kidney in, 17
 17-hydroxycorticosteroid metabolism in, 137
 serum citric acid in, 137
Ureterosigmoidostomy, and hyperchloremic acidosis, 126
Urine, and low potassium diet, 127
- Valsalva maneuver**, in pulmonary congestion, 115
Valve
 aortic, permanent by-pass of, 35
 mitral, kinetocardiography and ballistocardiography of, 70
Valvectomy, pulmonary partial, 109
Vasoconstriction, pulmonary, 35
Vectorcardiography
 of bundle branch block, 39
 in congenital heart disease, 108
 conventional leads in, 40
 in right bundle branch block, 108
 in ventricular hypertrophy, 109
Ventricular
 activity with quantitative EKY, 108
 function, study of, 109
Vitamin B₁₂
 deficiency in pernicious anemia, 28
 and intrinsic factor activity, 194
 in pernicious anemia, 7
 urinary excretion of, 28
- W-341**, 144
Water
 in blood, determination of, 63
 loads, in cirrhosis, 142
 secretion, into gastric juice, 205
 splanchnic exchangeable, 125
 tolerance, impaired, 44
- X-ray**
 cinematography, 107
 whole body, effects of, 148

ay]

93
in,

01
of,
od,

33
133

ab-

hy-
126
127

nary

f, 35
and
of,

, 109
35

108

, 108
109

ative

emis,

y, 194

63

e, 205
125

3